Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

SEPTEMBER--1960
Volume 10 - Number 9

009215

The gift of confidence in epilepsy. In the enchanted moment of childhood, happiness is a world of friends, plans, faces, teams . . . Time was when the penalty of being "different" was to be denied these joys of belonging, never to know the simplest and sweetest pleasures of growing up. Now, with these five distinguished anticonvulsants you can take your patients from early childhood to productive maturity—steadily, usefully, confidently.

Anticonvulsants by Abbott. PEGANONE® (Ethotoin, Abbott)—A hydantoin of exceptionally low toxicity. Indicated for *grand mal* and psychomotor seizures. **PHENURONE®** (Phenacemide, Abbott) —Often effective when other agents fail. For *grand mal*, *petit mal*, psychomotor and mixed seizures. **GEMONIL®** (Metharbital, Abbott)—Relatively non-toxic. For *grand mal petit mal*, myoclonic and mixed seizures symptomatic of organic brain damage. **TRIDIONE®** (Trimethadione, Abbott) **PARADIONE®** (Paramethadione, Abbott)—Homologous agents. Generally afford symptomatic control of *petit mal*, myoclonic and akinetic seizures.

ABBOTT

"the most effective drug against tremor..."[1]

IN PARKINSONISM Parsidol exceeds all other drugs for reducing tremor,[1] a major impairment in this disease. Parsidol also lessens rigidity, brightens the patient's mood and contributes to restoration of self-confidence. Especially well tolerated by older patients,[1,2,3] Parsidol is effective alone, and most patients respond well to a maintenance dosage of 50 mg. q.i.d. Parsidol is compatible with other antiparkinsonian drugs and can be given in combination if so desired.

PARSIDOL®

brand of ethopropazine hydrochloride

PARKINSONISM

WARNER CHILCOTT
MORRIS PLAINS, N.J.

1. Schwab, R. S. and England, A. C.: *J. Chron. Dis. 8*:488 (Oct.) 1958.
2. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
3. Doshay, L. J. *et al.: J.A.M.A. 160*:348 (Feb. 4) 1956.

PAR-GP04

Because it sustains relief of myasthenia gravis symptoms up to two and one-half times as long as the regular tablet, new MESTINON TIMESPAN often "eliminates the need for sleep interruption to take further medication and leads to better strength in the morning."* For treatment during waking hours, MESTINON TIMESPAN offers greater convenience, prolonged relief on fewer individual doses, and unprecedented freedom from muscarinic side effects.

DOSAGE: Timespan tablets—½ to 3 tablets once or twice daily.

HOW SUPPLIED: Tablets, 180 mg each—bottle of 100.

*K. R. Magee and M. R. Westerberg, **Neurology, 9**:348, 1959.

p-r-o-l-o-n-g-e-d relief in myasthenia gravis

Schematic drawing of nerve endings in striated muscle tissue. By inhibiting destruction of acetylcholine at this junction, Mestinon acts specifically to reestablish neuromuscular control and relieve symptoms of myasthenia gravis.

MESTINON® BROMIDE
—brand of pyridostigmin bromide
(3-hydroxy-1-methylpyridinium bromide)
TIMESPAN®

MESTINON TIMESPAN

in sustained release tablets—requires fewer individual doses

ROCHE LABORATORIES•Division of Hoffmann-La Roche Inc•Nutley 10, New Jersey

Volume 10 **Neurology** Number 9

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

OFFICERS

AUGUSTUS S. ROSE, M.D., *President*
A. L. SAHS, M.D., *President-Elect*
JOSEPH M. FOLEY, M.D., *Vice-President*
ROBERT UTTERBACK, M.D., *Secretary*
CHARLES M. POSER, M.D., *Treasurer*

BOARD OF EDITORS

Editor-in-Chief: RUSSELL N. DEJONG, M.D., *Ann Arbor, Michigan*
Associate Editor: MABEL G. MASTEN, M.D., *Miami, Florida*
Editorial Board: PEARCE BAILEY, M.D., *Washington, D.C.*
JOE R. BROWN, M.D., *Rochester, Minnesota*
ROLAND P. MACKAY, M.D., *Chicago, Illinois*
H. HOUSTON MERRITT, M.D., *New York, New York*
FRANK MORRELL, M.D., *Minneapolis, Minnesota*
JAMES L. O'LEARY, M.D., *St. Louis, Missouri*
CARL C. PFEIFFER, M.D., *Atlanta, Georgia*
ALFRED POPE, M.D., *Waverly, Massachusetts*
E. P. RICHARDSON, JR., M.D., *Boston, Massachusetts*
RICHARD B. RICHTER, M.D., *Chicago, Illinois*
J. PRESTON ROBB, M.D., *Montreal, Canada*
RAY S. SNIDER, M.D., *Chicago, Illinois*
JAMES E. P. TOMAN, M.D., *Chicago, Illinois*
DONALD B. TOWER, M.D., *Bethesda, Maryland*
ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*
A. EARL WALKER, M.D., *Baltimore, Maryland*
PAUL I. YAKOVLEV, M.D., *Boston, Massachusetts*

NEUROLOGY is published monthly at 84 So. Tenth St., Minneapolis 3, Minn., by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Second-class postage paid at Minneapolis, Minn.

In 8 out of 10 patients complete control of grand mal seizures with

"MYSOLINE"®

wide margin of safety

BRAND OF PRIMIDONE

COMPOSITE RESULTS OF 20 CLINICAL STUDIES

Results in 262 epileptic patients when "Mysoline" was used alone.

Type of Seizure	Number of Patients	Completely Controlled	50-90% Improved	<50%
Grand Mal	214	172 (80%)	15 (7%)	27 (13%)
Psychomotor	29	19 (65%)		10 (35%)
Focal Jacksonian	19	19 (100%)		

Results in 835 epileptic patients who had failed to respond successfully to other anticonvulsants. "Mysoline" was added to current medication which, in some cases, was eventually replaced by "Mysoline" alone.

Type of Seizure	Number of Patients	Completely Controlled	50-90% Improved	<50%
Grand Mal	613	175 (28.5%)	253 (41.2%)	185 (30.3%)
Psychomotor	130	10 (7.7%)	65 (50%)	55 (42.3%)
Focal Jacksonian	92	14 (15.2%)	36 (39.1%)	42 (45.7%)

The dramatic results obtained with "Mysoline" advocate its use as first choice of effective and safe therapy in the control of grand mal and psychomotor attacks. Literature and bibliography on request.

SPECIAL POTENCY NOW AVAILABLE

New 50 mg. small-dose tablet offers practical approach to dosage adjustment for initiation/combination/and "transfer" therapy in selected cases. Available on prescription.

Supplied: 0.25 Gm. (250 mg.) scored tablets, bottles of 100 and 1,000. Also 50 mg. scored tablets to facilitate dosage adjustment, bottles of 100 and 500.

AYERST LABORATORIES • New York 16, N. Y. • Montreal, Canada

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries, Ltd.

Volume 10 **Neurology** Number 9

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

SEPTEMBER 1960 • *Contents*

Studies of Tone, Tremor, and Speech in Normal Persons and Parkinsonian Patients 805
BENJAMIN BOSHES, M.D., HIRSH WACHS, M.D., JOEL BRUMLIK, M.D., MANUEL MIER, M.D., AND MATHEW PETROVICK, B.S.E.E.

Penetration of Radioactive Bovine Albumin from Cerebrospinal Fluid into Brain Tissue 814
J. C. LEE, M.B., M.Sc., AND J. OLSZEWSKI, M.D., Ph.D.

Meningeal Leukemia 823
RICHARD K. SHAW, M.D., EDWARD W. MOORE, M.D., EMIL J. FREIREICH, M.D., AND LOUIS B. THOMAS, M.D.

Cervical Disk Protrusions with Compression of the Spinal Cord 834
OLLE HÖÖK, M.D., HANS LIDVALL, M.D., AND KARL-ERIK ÅSTRÖM, M.D.

Adrenocortical Function in Epilepsy 842
PATRICK F. BRAY, M.D., ROBERT S. ELY, M.D., GERARDO ZAPATA, M.D., AND VINCENT C. KELLEY, M.D., Ph.D.

Interactions of Human Sera and Spinal Fluids with Antibrain Rabbit Sera 847
CLARA H. WILLIAMS, Ph.D., AND FREDERICK W. BARNES, Jr., M.D., Ph.D.

Regeneration of Peripheral Nerves with Hyperinsulin Neuronopathy 851
EDWARD H. LAMBERT, M.D., DONALD W. MULDER, M.D., AND JAMES A. BASTRON, M.D.

(Continued on next page)

NEUROLOGY, copyright 1960 by LANCET PUBLICATIONS, INC. Title registered U. S. Patent Office. Louis M. Cohen, Publisher. Allan Stone, Assistant to the Publisher. Mary Worthington Hoff, Managing Editor. Maurice Wolff, Business Manager, 84 S. 10th St., Minneapolis 3, Minn. ADVERTISING REPRESENTATIVES: *New York 17:* Burt D. Cohen, Lee Klemmer, Bernard A. Smiler, John Winter, 1 E. 42nd St. Telephone: Murray Hill 2-8717. *Chicago 6:* Greg Gelderman, Jay H. Herz, Hugh Gibson, 20 N. Wacker Drive, Suite 1462. Telephone: Central 6-4619. *San Francisco 4:* Duncan A. Scott & Co., 85 Post St., Fifth Floor. Telephone: Garfield 1-7950. *Los Angeles 57:* Duncan A. Scott & Co., 1901 West Eighth St. Telephone: Dunkirk 8-4151.

Contents—*Continued*

Case Report: Vertebral Artery Insufficiency Produced by Cervical Osteoarthritic Spurs 855
CREIGHTON A. HARDIN, M.D., WILLIAM P. WILLIAMSON, M.D., AND A. THEODORE STEEGMANN, M.D.

Pathogenesis of Cerebral Vasospasm in Hypertensive Encephalopathy
II. The Nature of Increased Irritability of Smooth Muscle of Pial Arterioles in Renal Hypertension 859
JOHN S. MEYER, M.D., ARTHUR G. WALTZ, M.D., AND FUMIO GOTOH, M.D.

Restless Legs Syndrome 868
K. A. EKBOM, M.D.

A Note on Warm and Cold Spots 874
R. F. KIBLER, M.D., AND P. W. NATHAN, M.D.

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russel N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota. News items related to the American Academy of Neurology or to the field of neurology in general are to be sent to Dr. Pearce Bailey, 4725 Sedgwick, N.W., Washington 16, D. C.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY. They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be unmounted glossy prints. Tables should be typed on separate sheets. The title of the article, name of author, and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number, and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

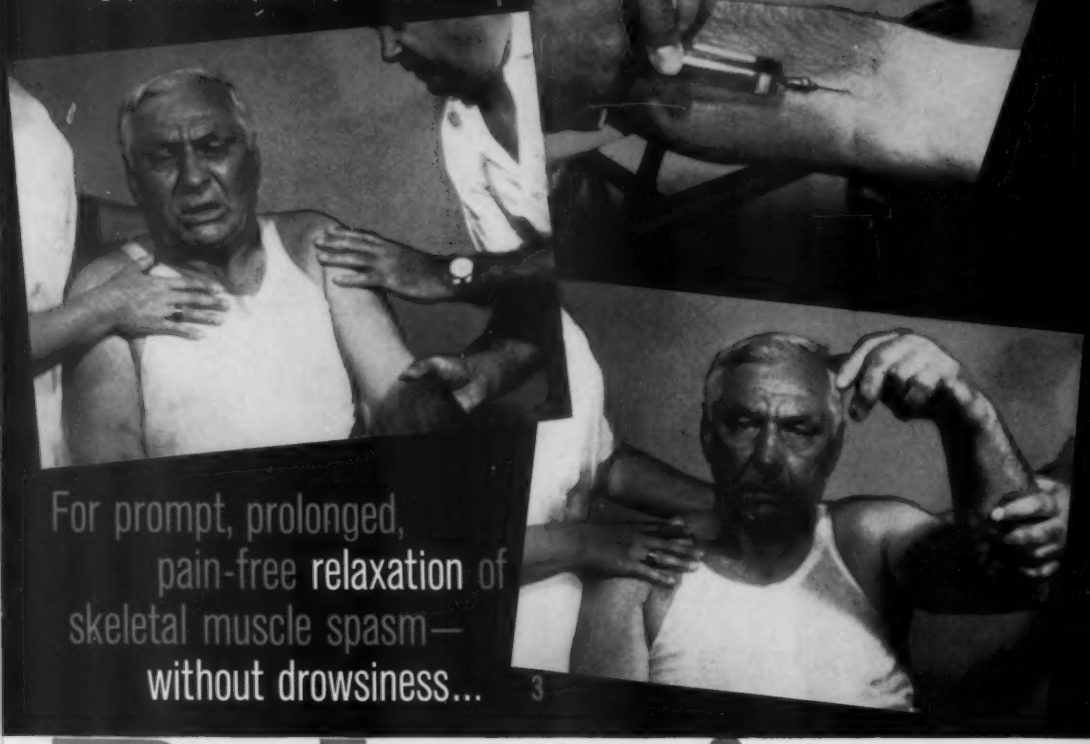
Journal reference: 1. FRANKLIN, C. R., and BRICKNER, R. M.: Vasospasm associated with multiple sclerosis. Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. WECHSLER, I. S.: A Textbook of Clinical Neurology, ed. 8. Philadelphia, W. B. Saunders Company, 1958, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

Factual Clinical Data: Male, 65, with dislocated shoulder; patient in great pain. Fifteen minutes after administration of 10 cc. of ROBAXIN Injectable, dislocation reduced on first attempt, and patient was able to move arm easily. Photographs used with patient's permission.



For prompt, prolonged, pain-free **relaxation** of skeletal muscle spasm— without drowsiness...

Robaxin®

Robins

Methocarbamol 'Robins' U.S. Pat. No. 2770649

ROBAXIN Injectable: for relaxation of painful spasm within minutes.

ROBAXIN Tablets: for initial relief, or to maintain relaxation originally induced by ROBAXIN Injectable. Virtually free from adverse side effects, including drowsiness.

Ten published studies show ROBAXIN Injectable and ROBAXIN Tablets beneficial in 91% of cases.[1-10] Literature available to physicians on request.

SUPPLY: ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50 and 500.

ROBAXIN Injectable, each ampul containing 1.0 Gm. of methocarbamol in 10 cc. of sterile solution.

A. H. ROBINS CO., INC., Richmond 20, Virginia

Making today's medicines with integrity . . . seeking tomorrow's with persistence

REFERENCES: 1. Carpenter, E. B.: Southern M. J. 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Grisolia, A., and Thomson, J. E. M.: Clin. Orthopaedics 13:299, 1959. 4. Hudgins, A. P.: Clin. Med. 6:2321, 1959. 5. Lewis, W. B.: California Med. 90:26, 1959. 6. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 7. Park, H. W.: J.A.M.A. 167:168, 1958. 8. Plumb, C. S.: Journal-Lancet 78:531, 1958. 9. Poppen, J. L., and Flanagan, M. E.: J.A.M.A. 171:298, 1959. 10. Schaubel, H. J.: Orthopedics 1:274, 1959.

how does* Mellaril *differ from other potent tranquilizers?

Mellaril®

THIORIDAZINE HCl

specific, effective tranquilizer

provides highly effective tranquilization,
relieves anxiety, tension, nervousness,
but is virtually free of such toxic effects as

jaundice
Parkinsonism
blood dyscrasia
dermatitis

greater specificity of tranquilizing action results in fewer side effects

Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action—divorced from such "diffuse" effects as anti-emetic action.

"Moderate to marked improvement in psychomotor behavior was obtained with Mellaril in 17 of the 22 cases in this series. In addition, there was complete elimination of extrapyramidal activity in 15 of 18 patients who had manifested Parkinsonian symptoms with the drugs previously employed. Our observations indicate that Mellaril is equally effective, or more so, than other phenothiazines in the treatment of various psychiatric disorders, but has a distinctly lessened tendency to induce extrapyramidal stimulation. In our experience, this is a significant contribution to the more effective management of larger numbers of disturbed patients."*

Supply: MELLARIL Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

*Khakee, A., and Hess, G. F.: Mellaril in the Treatment of Chronically Disturbed Patients: With Special Reference to Reduced Extrapyramidal Complications, Am. J. Psychiat. 116:1030 (May) 1960.

SANDOZ

NEW STIMULATORS

MODEL S 6

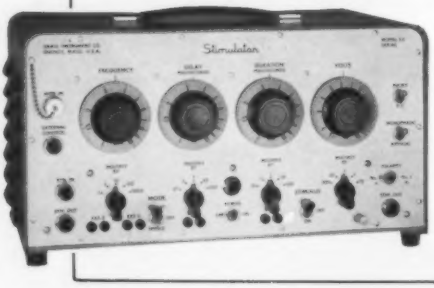
AN ECONOMICAL STUDENT STIMULATOR

MODEL S 5

IDEAL FOR STUDENT LABORATORIES, OPERATING ROOM USE AND MANY RESEARCH LAB APPLICATIONS

MODEL SD 5

SUITABLE FOR MOST RESEARCH PROBLEMS AND FOR ADVANCED STUDENT LABORATORY USE



MODEL S 4

FOR MAXIMUM VERSATILITY IN RESEARCH APPLICATIONS

GRASS INSTRUMENT COMPANY

101 OLD COLONY AVENUE - QUINCY, MASS.

INSTRUMENT MAKERS TO THE MEDICAL PROFESSION SINCE 1935

K901 P6

one child has epilepsy... even her companions might not know—if her seizures are controlled with medication

"...nowadays our approach should be, as far as possible, to protect the patient with sufficient medicine and allow him to live as much as possible the life of a normal child."*

for clinically proved results in control of seizures

DILANTIN® SODIUM KAPSEALS® *outstanding performance in grand mal and psychomotor seizures...* DILANTIN Sodium *(diphenylhydantoin sodium, Parke-Davis) is available in several forms, including Kapseals of 0.03 Gm. and of 0.1 Gm., in bottles of 100 and 1,000.*

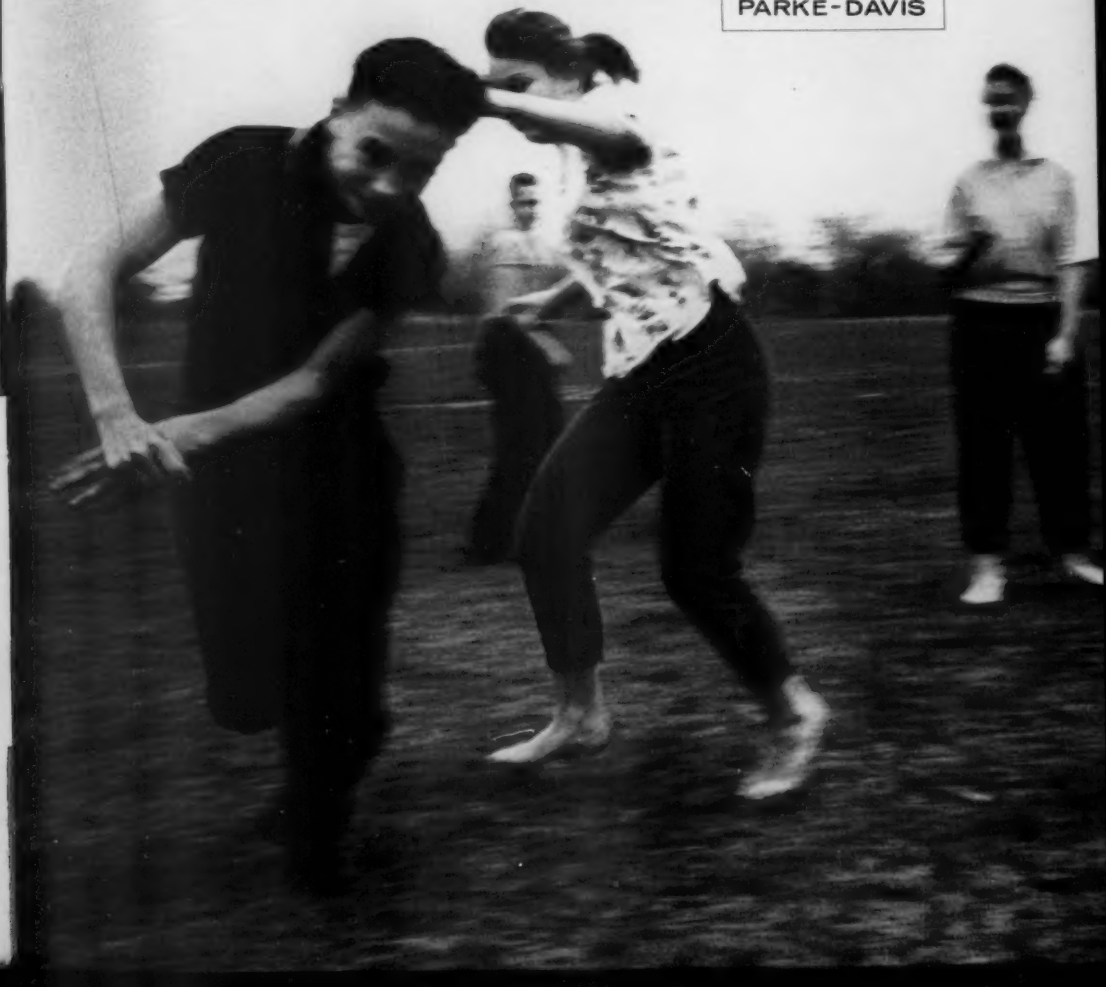
other members of THE PARKE-DAVIS FAMILY OF ANTICONVULSANTS
for grand mal and psychomotor seizures: PHELANTIN® Kapseals *(Dilantin 100 mg., phenobarbital 30 mg., desoxyephedrine hydrochloride 2.5 mg.) bottles of 100 · for the petit mal triad:* MILONTIN® Kapseals *(phensuximide, Parke-Davis) 0.5 Gm., bottles of 100 and 1,000; Suspension, 250 mg. per 4 cc., 16-ounce bottles.* CELONTIN® Kapseals *(methsuximide, Parke-Davis) 0.3 Gm., bottles of 100.*

Literature supplying details of dosage and administration available on request.

*Scott, J. S., & Kellaway, P.: M. Clin. North America 42:415 (March) 1958.

PARKE, DAVIS & COMPANY
Detroit 32, Michigan

PARKE-DAVIS



Dynamic Myelography

These two radiographs of the same patient demonstrate the bulging of the annulus fibrosus during hyperextension and flexion, respectively, of the vertebral column. 30 cc of ***Pantopaque*** contrast medium was used. Note how this technique permits visualization of the posterior surface of the vertebral canal.

"PANTOPAQUE" *is the registered trademark under which all leading x-ray dealers supply the compound ethyl iodophenylundecylate, which is synthesized by the Research Laboratories of Eastman Kodak Company and prepared as the myelographic contrast medium Iophendylate Injection, U.S.P., by Lafayette Pharmacal Inc. The trademark serves to indicate to the radiologist continuity of experience in the manufacture of this medium.*

when "Parkinson" reactions threaten in ataractic therapy . . .

add . . .

ARTANE®

Trihexyphenidyl HCl Lederle

ARTANE is repeatedly cited[1-4] as an effective adjunct to counter parkinsonoid side effects of phenothiazine therapy . . . to forestall withdrawal and secure the benefits of undiminished, uninterrupted, high-dosage therapy.

In Parkinson's disease, ARTANE remains a drug of choice in the experience of many practitioners. Unexcelled for sustained, continuing control of rigidity and tremors, suppression of other symptoms with low risk of untoward effects.

Elixir, 2 mg./5 cc. tsp.

Dosage: 1 mg. first day, gradually increased according to response, to 6-10 mg. daily in 3 divided doses at mealtimes.

1. Critchley, M.: **British, M. J.,** 2:1214 (Nov. 15) 1958.
2. England, A. C., and Schwab, R. S.: **A.M.A. Arch. Int. Med.** 104:439 (Sept.) 1959.
3. Judah, L., Murphree, O., and Seager, L.: **Am. J. Psychiat.** 115:118 (June) 1959.
4. Pennington, V. M.: **M. Times** 87:1432 (Nov.) 1959.

LEDERLE LABORATORIES,
Pearl River, New York
A Division of AMERICAN CYANAMID COMPANY

IN CORD BLADDER
long-term therapy with
MADRIBON
the safest long-acting sulfonamide

"...especially useful for long-term therapy required in persistent chronic infections."[1]

controls infection Madribon is effective in an unusually wide range of pathogens, including some antibiotic-resistant strains. "Excellent"[2] results were obtained in a group of 35 paraplegics—all with cord bladders, chronic cystitis and some degree of pyelonephritis for up to 15 years. During a full year on Madribon, despite **in vitro** resistance, none "...exhibited the clinical signs of bladder infection."[4]

safely With Madribon therapy, the incidence of side effects is exceptionally low — less than two per cent in over 15,000 reported cases. An impressive absence of side effects was especially noted in the extended treatment of paraplegics.[2,3]

economically Madribon is realistic therapy because of "... its effectiveness in low dosage and its long-acting potential."[2] The cost of Madribon "...is approximately one third that of the average antibiotic."[4]

References: 1. J. D. Young, Jr., W. S. Kiser and O. C. Beyer, **Antibiotic Med. & Clin. Therapy, 6**:(Suppl. 1), 53, 1959. 2. W. A. Leff, **ibid.**, p. 44. 3. R. E. Bagdon, L. O. Randall and W. A. Leff, **Ann. New York Acad. Sc., 82**:(Art. 1), 3, 1959. 4. J. C. Elia, **ibid.**, p. 52.

Consult literature and dosage instructions, available on request, before prescribing.

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc.

MADRIBON® — 2,4-dimethoxy-6-sulfanilamido-1,3-diazine

Neurology Volume 10 • Number 9

Studies of tone, tremor, and speech in normal persons and parkinsonian patients

I. Methodology

Benjamin Boshes, M.D., Hirsh Wachs, M.D., Joel Brumlik, M.D., Manuel Mier, M.D., and Mathew Petrovick, B.S.E.E.

THE URGENT NEED for objective methods of recording the phenomena of the parkinsonian state has led to the development of instruments and procedures to measure tone, tremor, and voice in this symptom complex. Analyses of these records may throw new light on fundamental neuropathophysiology.

REVIEW OF LITERATURE

In general, methods of evaluating muscle tone utilize either active or passive resistance. Only the latter are subject to quantitation. Tension of voluntarily relaxed muscle can be measured by 3 methods:

1. Those which measure "hardness" of a muscle. These are inaccurate due to errors introduced by subcutaneous tissues. Moreover, the units of measurement are not those of muscle tension.[1–15]

2. Electromyography, which can measure muscle tone only indirectly and the parameters of which are, again, not those of tension.[16–19]

3. Apparatus designed to measure tone by determining the force required to bend a voluntarily relaxed limb.[20–23] This is most precise. Methods employing the horizontal plane of motion are more reliable than those using the vertical.[24–29] The most accurate devices are those employing a constant velocity of limb motion to eliminate inertial factors.[30–36]

In all, 5 different methods have been used to record tremor. The first was the tambour, employing a combination of pneumatic and mechanical devices to transmit the forces created by tremor to a write-out system.[37–43] Numerous modifications employ beams of light, mirrors, and optical devices for recording.[32,44–49] Others utilize strain gauges. The forces being

From the Department of Neurology and Psychiatry, Northwestern University Medical School, Chicago.

This study was aided by Grant B-1421 from the National Institute of Neurological Diseases and Blindness, Bethesda, Md.

Read at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 16, 1959.

measured upset the balance of a bridge arrangement, giving rise to recordable electrical output.[30,50] Tremor has been measured by electromyographs employing surface or intramuscular electrodes.[16–19,51] Finally, methods utilizing the principle of variable reluctance of an iron core moving in a magnetic field have been devised.[30,52] The last method, which has been found to be most satisfactory, is used in this study.

DEFINITION OF TERMS

For the purpose of this investigation, the following definition of tone is used:[53] "Tone is a long-continued state of tension in a muscle maintained by the activity of the contractile elements." Tension is defined as "stress on a material caused by pulling."

Tremor is defined as a descriptive symptom consisting of any oscillatory movement of a part of the body, be it regular or irregular, fine or gross, constant or periodic, or present at rest or on activity. In this study, tremor will be measured in extremities placed in different positions according to the criteria outlined by Bucy.[54] Tremor at rest is that in an extremity supported against gravity. Static tremor is that in an extremity held still by the subject, using only the muscles in the limb involved but not supported against gravity.

REQUIREMENTS OF IDEAL RECORDING SYSTEM

A system for recording tremor and tone ideally should fulfill the following requirements:

- Measurement of tremor and tone separately should be possible, using different and discrete write-out systems.
- Measurement of tremor and tone in the same limb must be possible.
- The operation of the system should not be painful.
- The system should not be complicated in operation or appearance. This is to keep the anxiety of the patient at a minimum.
- The system should not require darkening of the room or performance of other maneuvers that might distract the patient.
- The system must be accurate and capable of calibration, and the results must be reproducible.
- The system should record tremor and tone directly, not a value that may be proportional to them, such as bursts of electromyographic potentials.

In addition, the method for the measurement of tone should include these specifications:

- Tension of isolated muscle groups should be recorded in absolute units of force.
- Tone should be measured during motion of an extremity in the horizontal plane.
- The procedure should be designed to eliminate voluntary tension and phasic reflexes in the muscles studied.
- Tone must be measured during a constant velocity period of limb motion so that the mass of the limb will add no torque to that produced by muscle tension per se.

The method for measuring tremor should also include the following qualifications:

- The system should measure linear tremor in one plane only, not a vector sum of tremor in different directions.
- The system should not add to the inertia of the part of the body being tested.
- The system should be adaptable so that recordings can be made from different parts of the body without awkward positioning of the measuring device or the patient.
- The system should be capable of measuring more than one tremor at the same time, that is, able to measure tremor in different areas of the body or different planes of the same area simultaneously.
- The measuring device should be easily attachable and removable from the area studied.
- The system should be capable of recording not only frequency of tremor but also amplitude and wave-form characteristics over all ranges of amplitude. This necessitates great sensitivity, to measure fine tremor, as well as proper control, to record tremor of great magnitude.
- The system should lend itself to automatic electronic analysis of frequency and amplitude, should this be desired.
- The system should write out the tremor waves in such a manner that the recording can be preserved for later study with all the temporal relationships intact.

A system for the study of voice alterations should include not only the evaluation of the mechanisms involved in the production of speech but also a survey of the functions of

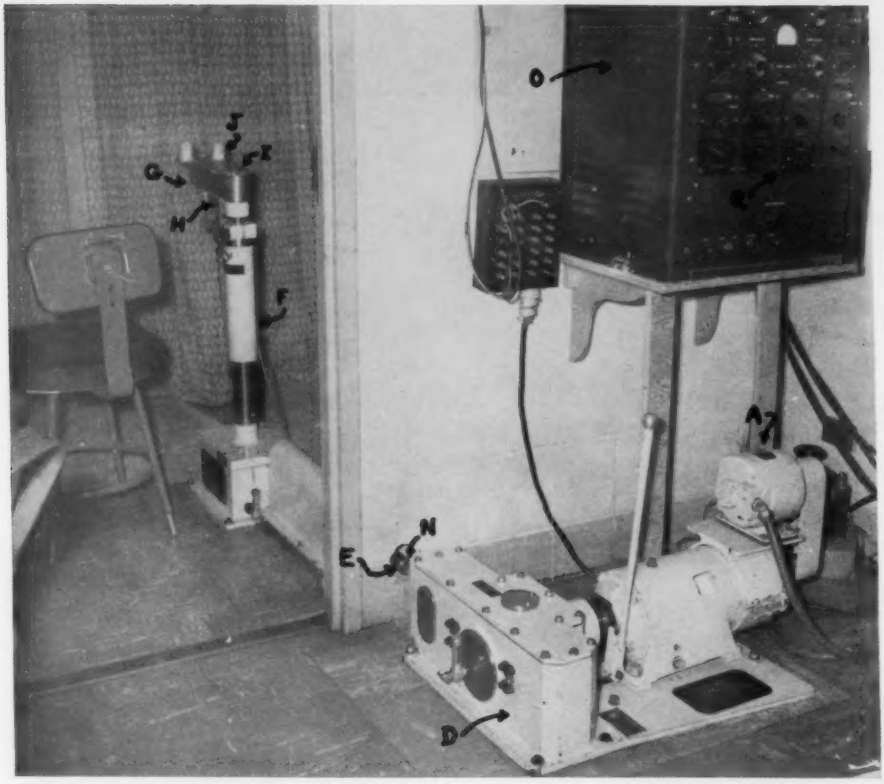


Fig. 1. General view of the tonometer, showing motor, tone arm, and console. See text for further explanation.

the central nervous system and the perception of auditory signals. The system will therefore include instruments for the study of the phenomena of articulation, phonation, breathing, and the auditory monitoring system.

METHODOLOGY

The entire apparatus to measure tone is designed to move an arm board (Figs. 1 and 2 [G]) through a constant arc of 55°. An electric motor [A] drives the arm board in a continuous to-and-fro motion. Guides [J] are made of small aluminum rods covered with foam rubber. They serve only to prevent the wrist from slipping off the arm board. The guide hole [I] is a shallow cup machined over the axis of turning of the column [F]. The medial epicondyle of the tested arm is placed in this cup during the procedure. This provides a means whereby the axis of bending of the elbow is kept over the axis of turning of the tone arm. The spring steel bar [H] is the sole link between the tone arm [G] and supporting pillar [F]. Thus, any torque on the tone arm is transmitted entirely to this bar. Bonded symmetrically to both sides of the bar [H] are 4 strain gauges, 2 on each side. The gauges are connected in the form of a Wheatstone bridge, the output of which is fed to the first channel of a direct-writing oscillograph via an input coupler [Q]. A potentiometer [N], which is fixed to the housing [D], is mechanically coupled to a cam follower from the moving shaft [E]. The output of the potentiometer is

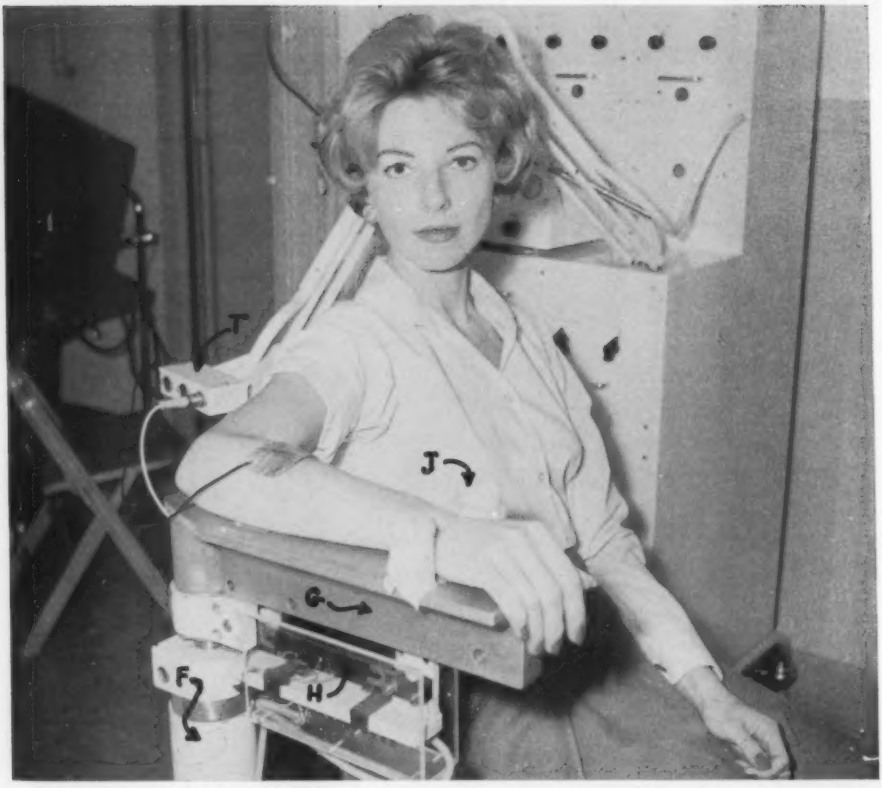


Fig. 2. Patient seated at tonometer, showing strain gauge arrangement, position of arm, and electromyograph. See text for further explanation.

recorded via an input coupler [Q] on the second channel of the oscillograph. The velocity of the tone arm [G] is controlled from a drive box. As the shaft [E] describes a to-and-fro linear motion, the signal from the potentiometer is altered in proportion to the degree of motion of the shaft, so as to produce a pure sine wave on the tracing (Fig. 3). The pen of the first channel (torque signal) is centered on a fixed base line at the start of testing. Any deflection from the base line is proportional to a torque exerted on the tone arm. The midpoint of the arc of motion is a point of constant velocity at which all measurements are taken. The machine is calibrated by measuring the torque produced by known weights attached to the tone arm.

The equipment used for the recording of tremor consists of 3 basic units. That which senses the movement is the accelerometer. The second amplifies the output of the accelerometer and prepares it for recording. The final section, which does the actual recording, is a direct-writing oscillograph. The accelerometer used is the Glennite AVR-250 (manufactured by Gulton Industries, Inc., Metuchen, N. J.), which is designed to measure low frequency vibrations and accelerations on small structures. It is essentially a variable reluctance pickup. A console (Fig. 1 [Q]) houses the necessary equipment to balance and calibrate a bridge, the carrier oscillator, an input amplifier, a phase splitter, a push-pull amplifier, a phase-sensitive demodulator, and an input coupler.

Special sensitivity controls and other modifications as necessary to achieve the special signal clarity desired are built into the unit. The system employs the common design technics used in the field of guided missiles, with new application to the field of tremor measurement. This was first done by Agate, Doshay, and Curtis.[30]

In the measurement of the components of voice, the following equipment is employed: Breathing is measured by use of a spirometer, pneumograph, pneumotachograph, gas analysis apparatus, and *p*H meter. Speech is recorded on magnetic tape in a sound-treated room. The tapes are subsequently analyzed with appropriate instrumentation, including a power level recorder and a phonation timer.

PATIENT SELECTION

Persons to be tested were placed in 2 groups of 30 members each. The first were controls, adults free of neurologic disease. The second were patients with clinical parkinsonism. Both groups were equivalent as to age. No subject who had significant bone or joint disease was included. All treatment for the parkinsonism patients was suspended for at least twenty-four hours before recording.

Patients who exhibited alterations of the speech organs, such as after surgery, or whose peripheral hearing was below normal limits for their age were excluded from speech studies.

PROCEDURE

When tone was measured, the patient was seated at the tone arm, as in Figure 2. He was instructed to relax. The pen of channel A was centered on the base line. The tone-arm motion proceeded at a constant speed of 2.5 strokes per minute. Extension and flexion of both upper extremities were recorded. The deflection of the pen from the base line at the midswing was measured for each of 10 trials (extension and flexion of the right and left arms). The means of these 40 values were converted to torque expressed in dyne-centimeters by means of a calibration graph. Surface electromyography (Fig. 2 [T]) from the triceps muscle of the tested arm was used as a monitor of voluntary resistance. Any trial in the controls showing such voluntary resistance was eliminated.

For measurement of tremor, the accelerometer was taped onto the proximal phalanx of the index finger when the upper extremity was tested and onto the proximal phalanx of the great toe when the lower extremity was tested. Before recording, both accelerometers were placed on the same finger and the gain settings balanced, so that both channels produced the identical tremor amplitude. This was necessary because of the slight difference in the writeout of the channels. Although both operate independently and are equally sensitive, the inevitable differences in component characteristics of the channels result in slight differences in amplitude of signal at the same gain settings. The extremities were placed in one of two positions during testing. They were held in either the rest position, in which the extremity was supported, or the up position, in which the patient voluntarily elevated the extremity, holding it out in front of him, not supported against gravity. For the upper extremity, the rest position consisted of the forearm lying on a flat surface with the wrist and hand hanging over the edge. The edge of the supporting surface came to a point 1 in. proximal to the radial styloid. Figure 4 shows the patient sitting with both hands at rest. For the lower extremity, the rest position con-

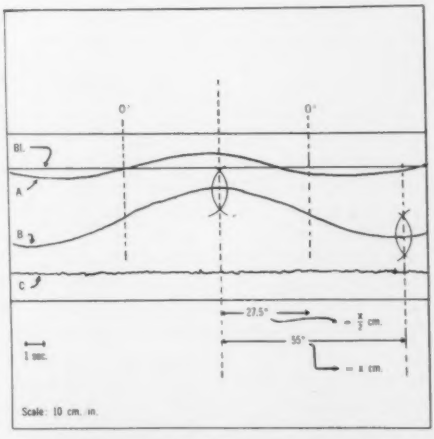


Fig. 3. Diagram of normal torque plot. B.L. =baseline. A=torque signal from strain gauges. B=potentiometer plot. C=signal from electromyograph

Fig. 4. Upper extremities in rest position

Fig. 5. Left upper extremity in up position

sisted of the leg lying on a low chair with the ankle and foot unsupported.

In order to measure static tremor, the extremity was raised to the up position. Figure 5 shows the upper extremity in this position. For the lower extremity, the up position consisted of the patient's raising the extremity from the chair and holding it still, not supported against gravity. By a combination of 88 steps, the resting and static tremor of all 4 extremities was recorded when the extremities not being measured were at rest and in the up position. In addition, the vertical and horizontal planes of tremor in both upper extremities were recorded simultaneously. In order to derive the most information possible from this study, 2 accelerometers were always recording, at times from both upper extremities, at times from both lower extremities, and at other times from an upper and a lower limb. When both vertical and horizontal planes of upper extremity tremor were recorded, one accelerometer was taped to the dorsum of the finger and the other to the side of the finger. The control and experimental groups were tested with essentially the same protocol. In one series of tests, both vertical and horizontal planes of the same hand were recorded. However, in all other testing, when 2 extremities were measured, the vertical plane only was recorded. Thus, not only is the tremor of an extremity recorded, but the study also includes the effect upon this tremor when that extremity was raised voluntarily against gravity. Also studied was the effect of tremor in the resting extremity and in the raised limb when other limbs, singly and in various combinations, were raised.

The patients in whom voice was measured were given a thorough otorhinolaryngologic examination, including speech and pure-tone audiometry. A battery of pulmonary function studies, including analysis of the arterial blood for carbon dioxide, oxygen, and *p*H, was performed. Finally, in a sound-treated room and under standardized conditions, a series of special speech tests was administered. These included the reading of a phonetically balanced passage, articulatory diadochokinetic rates, sustained vowels, and voluntary vocal pitch and intensity ranges. The data were then analyzed in terms of articulation, intensity, frequency, and temporal aspects.

RESULTS

Figure 3 shows a diagram of the torque plot in the normal patient. The mean torque in dyne-centimeters is recorded, resulting in 4 mean values per patient per testing day: torques of flexion and extension of right and left upper extremities.

Tremor is analyzed according to 8 parameters. Each of the 88 steps of the test procedure is measured in the following manner:

Dominant frequency is analysed by the visual method and expressed in cycles per second.

Frequency regularity is an expression of frequency regularity and degrees of irregularity. A regular tremor, given the symbol R, has a

predominantly regular frequency (Fig. 6). There are 3 degrees of irregularity. A tremor predominantly mildly irregular is given the symbol I; a tremor predominantly moderately irregular is given the symbol I+; and a tremor predominantly severely irregular is given the symbol I++.

Mode amplitude is an expression in millimeters of the average peak-to-peak amplitude.

Amplitude regularity expresses the amplitude regularity and degrees of irregularity in the same fashion and by the same symbols used in analyzing frequency regularity, as described above. Figure 6 again illustrates the varieties of amplitude regularity.

Amplitude periodicity describes a spontaneous waxing and waning effect of the amplitude and is not to be confused with amplitude irregularity. A tremor may have an irregular amplitude but may be constantly perpetuated. Periodicity describes a situation in which the amplitude increases and decreases periodically over a relatively long stretch of the record. A tremor of any degree of amplitude irregularity may or may not be periodic. Figure 7 illustrates a periodic tremor that is waxing and waning. Each channel of each step is analyzed for either the presence or the absence of periodicity.

Harmonics refers to consistently reproduced spontaneous wave activity that bears a definite temporal relationship to the basic frequency. Figure 8 illustrates some different forms taken by harmonic activity. Again, each step is analyzed for presence or absence of harmonics.

Spindles are described as spontaneous oscillatory activity of the tremor forms themselves, somewhat of a periodic effect occurring regularly (Figure 7). This has some similarities to the amplitude periodicity concept but is described separately because it occurs with more regularity and may appear apart from amplitude periodicity.

Abrupt wave-form change describes the phenomenon of abrupt spontaneous change in the wave form from regularity to irregularity or vice versa (Fig. 7).

Some of these parameters of tremor involve quantitative measurements of phenomena with varying degrees of irregularity. Other parameters involve actual measurements of frequency or amplitude. Still others involve "yes" or "no" responses, with no attempt being made to quantitate degree of incidence in an individual step.

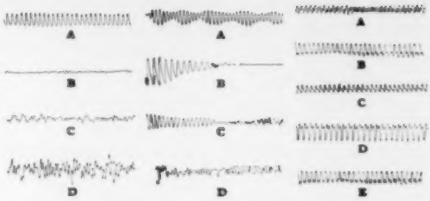


Fig 6. *(Left)* Degrees of tremor frequency and amplitude regularity. [A] Regular. [B] Mildly irregular. [C] Moderately irregular. [D] Severely irregular

Fig. 7. *(Center)* Tremor parameters. [A] Spindles. [B] Amplitude periodicity. [C] and [D] Abrupt wave-form change in regularity

Fig. 8. *(Right)* Harmonics in tremor tracings

DISCUSSION

To our knowledge, the equipment described is the most sensitive and accurate that has thus far been used for the recording and measurement of tone and tremor.

No previous studies of tone and tremor have employed the parameters of measurement utilized herein. It is believed that these parameters are of greater significance in defining these phenomena than are the traditional methods that utilize frequency and amplitude only. The parameters of tone quantitate muscle tension in absolute units, dyne-centimeters. These methods of measurement of both tone and tremor have proved valid and reliable.

Variables that affect tone and tremor have been considered and will be presented in a future report. The incidence of the parameters of tone and tremor in normal persons and in patients with parkinsonism will also be presented.

Preliminary studies of voice have suggested that several measurements of the abnormal speech in patients with Parkinson's disease are indicative of the differences between this clinical group and normal speakers. The intensity and time components appear to be

especially sensitive to distortion in this condition. A more detailed presentation of the quantification of these deviations will appear in future reports.

Evaluation of the respiratory mechanism, which provides the energy essential for the production of voice, is basic to our study. The altered anatomy and physiology of the respiratory system concomitant with parkinsonism have not been adequately investigated. The role of alterations of carbon dioxide, oxygen, and *p*H in affecting the symptoms of parkinsonism needs elucidation. The latter factors may have great significance.

SUMMARY

1. A methodology for the recording and quantitation of tone and tremor has been described.

2. Tone is measured by a strain gauge tonometer in dyne-centimeters of torque as the upper limb is moved through a constant arc, under controlled conditions.

3. Tremor is recorded by use of a variable reluctance accelerometer, an input coupler, and an inkwriter and is measured in terms of several new parameters.

4. A comprehensive study of the component factors of voice has been outlined.

Photographs reproduced by permission of Offner Electronics, Inc., General Electric Co., and Verson All Steel Co., Chicago, and Gulton Industries, Inc., Metuchen, N. J.

REFERENCES

1. Bajusz, E.: Experimentelle Untersuchungen mit Myotonometer und Myotonograph im Kindlesalter. Kinderärtze Praxis 22:486, 1954.
2. Exner, A., and Tandler, J.: Ueber die Messung des Muskeltonus und die Bedeutung des Tonus. Mitt. a. d. Grenzgeb. d. Med. u. Chir. 20:458, 1909.
3. Gildemeister, M., and Hoffmann, L.: Über Elastizität und Innendruck der Gewebe. Pflüger's Arch. f. d. ges. Physiol. 195:153, 1922.
4. Golla, F. L.: The objective study of neurosis. Lancet 201:115, 1921.
5. Hosiosky, A.: Experimentelle Untersuchungen über Muskelhärte und Tonus beim Menschen. Ztschr. f. d. ges. exper. Med. 39:462, 1924.
6. Kauffmann, F.: Untersuchungen über die Muskelhärte. Über Beziehungen zwischen Spannungsänderung und änderung der Härte (der elastischen Eigenschaften) beim lebenden menschlichen Skelettmuskel. Ztschr. f. d. ges. exper. Med. 29:443, 1922.
7. Lewy, F. H., and Kinderman, K.: Beziehungen zwischen Muskelhärte und Tonus. Ztschr. f. d. ges. Neurol. u. Psychiat. 80:390, 1923.
8. Mangold, E.: Untersuchungen über Muskelhärte. I. Mitteilung eine allgemein anwendbare Methode zur physiologischen Härtebestimmung. Pflüger's Arch. f. d. ges. Physiol. 196:208, 1922.
9. Mel'nikova, G. M.: Modification of the method of study of muscular tone. Sovet. Med. 22:89, 1958.
10. Mueller, R.: Die Härte menschlicher Muskeln bei Ruhe und Arbeit. Pflüger's Arch. f. d. ges Physiol. 206:106, 1924.
11. Noyons, A., and Uexkull, J. v.: Die Härte der Muskeln. Ztschr. f. Biol. 56:139, 1911.
12. Plaut, R.: Beobachtungen zur Sperrung des Skelettmuskels. Pflüger's Arch. f. d. ges. Physiol. 202:410, 1924.
13. Plotnikova, O. V., and Shafer, I. I.: A portable tonometer for the study of human muscles. Fiziol. zhur. Moscow 40:495, 1954.
14. Schade, H.: Gewebselastometrie zu klinischen und allgemeinärtzlichem Gebrauch. München. med. Wschnr. 53:2241, 1926.
15. Springer, R.: Untersuchungen über die Resistenz (die sogenannte Härte) menschlicher Muskeln. Ztschr. f. Biol. 63:201, 1914.
16. Hoefer, P. F. A.: Innervation and tonus of striated muscle in man. Arch. Neurol. & Psychiat. 46:947, 1941.
17. Hoefer, P. F. A., and Putnam, T. J.: Action potentials of muscles in rigidity and tremor. Arch. Neurol. & Psychiat. 43:704, 1940.
18. Hoefer, P. F. A., and Putnam, T. J.: Action potentials of muscles in spastic conditions. Arch. Neurol. & Psychiat. 43:1, 1940.
19. Hoefer, P. F. A., and Putnam, T. J.: Action potentials of muscles in normal subjects. Arch. Neurol. & Psychiat. 42:201, 1939.
20. Leibowitz, O.: Zur Frage des Tonus bei geführten Bewegungen. Deutsche Ztschr. f. Nervenh. 82:314, 1924.
21. Mosso, A.: Description d'un myotonométre pour étudier la tonicité des muscles chez l'homme. Arch. ital. d. biol. 25:349, 1896.
22. Reijs, J. H. O.: Über die Veränderung der Kraft während der Bewegung. Pflüger's Arch. f. d. ges. Physiol. 191:234, 1921.
23. Spiegel, E. A.: Zur Physiologie und Pathologie des Skelettmuskeltonus. Ztschr. f. d. ges. Neurol. u. Psychiat. 81:517, 1923.
24. Berkwitz, N. J.: Quantitative studies on the human muscle tonus. II. An analysis of 82 normal and pathologic cases. Arch. Neurol. & Psychiat. 28:603, 1932.
25. Boshes, B., and Norton, A. H.: Graphic studies in tone and tremor. Quart. Bull. Northwestern Univ. M. School 29:314, 1955.
26. Filimonoff, I. N.: Klinische Beitrage zum Tonus Problem. Ztschr. f. d. ges. Neurol. u. Psychiat. 96:368, 1925.
27. La Joie, W. J., and Gersten, J. N.: An objective method of evaluating muscle tightness. Arch. Phys. Med. 33:595, 1956.
28. Paskind, H. A.: Effect of laughter on muscle tone. Arch. Neurol. & Psychiat. 28:623, 1932.
29. Pollock, L. J., and Davis, L.: Relation of modifications of muscle tonus to interruption of certain anatomic pathways. Arch. Neurol. & Psychiat. 28:586, 1932.
30. Agate, F. J., Doshay, L. J., and Curtis, F. K.: Quanitative measurement of therapy in paralysis agitans. J.A.M.A. 160:352, 1956.
31. Fenn, W. O., and Garvey, P. H.: The measurment of the elasticity and viscosity of skeletal muscle in normal and pathologic cases; a study of so-called "muscle tonus." J. Clin. Invest. 13:383, 1934.
32. Fleisch, A., and Grandjean, E.: Der Tonus der Skelettmuskulatur im Hohenklima. Helvet. physiol. acta 6:474, 1948.
33. Schaltenbrand, G.: Über die Bedeutung der Myo-

graphie für die Begutachtung Nervenkranker. Med. Klin. 32:1148, 1936.
34. SCHALTENBRAND, G.: Myographische Untersuchungen in der Klinik. Geschichte der Myographie und Beschreibung eines neuen Myographen. Deutsche Ztschr. f. Nervenh. 142:1, 1937.
35. SCHALTENBRAND, G.: Myographische Untersuchungen in der Klinik. Messungsergebnisse bei gesunden Menschen. Deutsche Ztschr. f. Nervenh. 143:1, 1937.
36. SCHALTENBRAND, G.: Die Muskelspannungmessung (Myographie) und ihre Bedeutung für die klinische Diagnostik. Zentralbl. f. inn. Med. 1:1, 1940.
37. CHARCOT, J. M.: Clinical Lectures on Diseases of the Nervous System. Translated by T. Savill, London, The New Sydenham Society, 1889. Vol. 3, pp. 186-197
38. ESHNER, A. A.: A graphic study of tremor. J. Exper. Med. 2:301, 1897.
39. GRIMMER, R. V., and LANGWORTHY, O. R.: Apparatus to record movement of extremities. J. Lab. & Clin. Med. 26:1344, 1941.
40. MAREY, E. J.: Du mouvement dans les funtions de la vie. Paris, German Baillicre, 1868.
41. MORRIS, A. A., JR.: Apparatus to be used in recording tremors. Arch. Neurol. & Psychiat. 49:123, 1943.
42. SCHAFER, E. A.: On the rhythm of muscular response to volitional impulses in man. J. Physiol. 7:111, 1886.
43. WOLFENDEN, R. N., and WILLIAMS: A note on the rhythm and character of certain tremors. Brit. M. J. 1:1049, 1888.
44. BEALL, C. G.: New method of recording muscular tremors. Arch. Neurol. & Psychiat. 14:751, 1925.
45. CARPENTER, M. B., WHITTIER, J. R., and METTLER, F. A.: Tremor in rhesus monkey produced by diencephalic lesions and studied by graphic method. J. Comp. Neurol. 93:1, 1950.
46. COOPER, J. D., HALLIDAY, A. M., and REDFEARN, J. W. T.: Apparatus for the study of human tremor and stretch reflexes. Electroencephalog. & Clin. Neurophysiol. 9:546, 1957.
47. MEHRTENS, H. G., and POUPPIRT, P. S.: Recording of tremor—a new method. California & West. Med. 29:184, 1928.
48. REDDING, F., and GAMMON, G. D.: A new device for recording motion in 3 dimensions with illustrative application to the study of tremor Tr. Am. Neurol. A. 79:210, 1954.
49. REDFEARN, J. W. T.: Frequency analysis of physiological and neurotic tremors. J. Neurol. Neurosurg. & Psychiat. 20:302, 1957.
50. TUTTLE, W. W., JENNEY, C. D., WILKERSON, D. J., and IMIG, C. J.: Effect of exercises of graded intensity on neuromuscular tremor as measured by strain gauge technique. J. Appl. Physiol. 3:732, 1935.
51. BRAZIER, M. A. B.: Tremors of combat neuroses; comparison with tremors of paralysis agitans, delirium tremens and the psychoneuroses of civilian life; electromyographic studies. Arch. Neurol. & Psychiat. 54:175, 1945.
52. MARSHALL, J., and WALSH, E. G.: Physiologic tremor. J. Neurol. Neurosurg. & Psychiat. 19:260, 1956.
53. REMINGTON, J. W., ed.: Tissue Elasticity. Washington, D. C., American Physiological Society, 1957.
54. BUCY, P. C.: Neural mechanisms of athetosis and tremor. J. Neuropath. & Exper. Neurol. 1:224, 1942.

Penetration of radioactive bovine albumin from cerebrospinal fluid into brain tissue

J. C. Lee, M.B., M.Sc., and J. Olszewski, M.D., Ph.D.

IT IS USUALLY stated that certain substances of small molecular size can penetrate easily into the brain tissue from the cerebrospinal fluid, although they cannot pass the blood-brain barrier. According to Bakay,[1] this penetration is possible only when the particle radius of the substance is less than 10 Å. However, Bowsher[2] found that large molecules of radioactive proteins could enter the brain tissue along the blood vessels and also observed a slight, diffuse radioactivity in the subpial tissue. Mandelstamm and Krylow[3] considered that the penetration of substances from the cerebrospinal fluid into the brain was due to the flow of cerebrospinal fluid in the Virchow-Robin space. Davson[4] believed that simple diffusion through the mesothelial lining of the subarachnoid space and through the ependyma of the ventricles played a significant part. Bakay[1,5] noticed that penetration through the ependyma was dependent on changes in cerebrospinal fluid pressure. He found that withdrawal of cerebrospinal fluid followed by intracisternal injection of radioactive phosphorus (P^{32}) gave rise to radioactivity in the ependymal lining and that, after identical injection without withdrawal of cerebrospinal fluid, no radioactivity was seen there. It can be added that some investigators[6] have considered that the apparent difference in the penetration of substances into the brain tissue from blood and cerebrospinal fluid may be due only to the inappropriate selection of the dosage, which was considerably higher when the cerebrospinal fluid route was used.

The purpose of the present investigation was to study the penetration of radioactive iodinated albumin from the cerebrospinal fluid into the brain tissue. In particular, we were interested in finding out how deeply the albumin would penetrate into the nervous tissue, how long it would remain there, and whether such penetration would occur uniformly throughout the whole pial surface of the central nervous system.

MATERIAL AND METHODS

For these experiments, 20 adult rabbits, 6 dogs, and 3 cats of both sexes were used. Radioactive iodinated bovine albumin was employed as the tracer. Under Nembutal anesthesia, the animals received a suboccipital injection of 0.2 to 1 cc. of 2% tracer solution, corresponding to radioactivity of 20 to 250 μc. In some experiments, an equal amount of cerebrospinal fluid was withdrawn before the injection; in others, no such withdrawal was made. At various time intervals—twenty minutes to twenty-four hours after the injection—the animals were killed with an overdose of Nembutal. The brains were removed and fixed in 10% formalin overnight, and frozen sections 75 μ thick and, in 1 rabbit, serial paraffin sections 20 μ thick were prepared and mounted. Contact autoradiographs with no-screen x-ray film were made as reported elsewhere.[7] Histologic sections were stained by the Nissl method and, in a few instances, with hematoxylin-eosin.

RESULTS

The main results of our experiments are summarized in the table. As can be seen from this table and the accompanying figures, the leptomeninges, superficial subpial brain tissue, and some blood vessels became radioactive after subarachnoid injection of iodinated al-

From the Laboratory of Experimental Neuropathology, Department of Pathology, University of Saskatchewan, Saskatoon.

This work was supported by a grant from the Canadian National Research Council.

DISTRIBUTION OF RADIOACTIVITY AFTER SUBARACHNOID INJECTION OF THE TRACER

Experiment number and animal's weight	Volume and strength of tracer injected	Survival time after injection	Distribution and intensity of radioactivity					Figure numbers
			Lepto-meninges	Subpial brain tissue	Cerebral blood vessels: Sub-pial	Deep	Hippo-campal	
Rabbit 232 3.4 kg.	0.2 cc. 22 μc.	20 minutes	++	—	++	+	++	1 and 2
Rabbit 432 4 kg.	0.38 cc. 20 μc.	1½ hours	++	++	++	+	++	3
Cat 453 3 kg.	0.38 cc. 20 μc.	1½ hours	++	+	+	—	—	
Rabbit 448 4 kg.	0.2 cc. 20 μc.	3 hours	+++	+++	++	++	++	4
Rabbit 465 3.8 kg.	0.2 cc. 20 μc.	3 hours	+++	+++	++	++	++	
Rabbit 437 2 kg.	0.2 cc. 40 μc.	3 hours	++++	++++	+++	+++	+++	5
Rabbit 197 1.8 kg.	0.2 cc. 40 μc.	3 hours	++++	++++	+++	+++	+++	
Rabbit 479 4.5 kg.	0.4 cc. 40 μc.	3 hours	++++	++++	+++	+++	+++	
Cat 439 2.5 kg.	0.2 cc. 40 μc.	3 hours	+++	++	++	++	—	6
Cat 563 3.3 kg.	0.17 cc. 50 μc.	3 hours	+++	++	++	+++	—	
Dog 562 6 kg.	0.33 cc. 100 μc.	3 hours	+++	+++	++	++	—	7
Dog 623 5 kg.	1 cc. 250 μc.	3 hours	++++	++++	+++	+++	—	
Dog 624 6.5 kg.	1 cc. 250 μc.	3 hours	++++	++++	+++	+++	—	8 and 9
Rabbit 444 3.1 kg.	0.34 cc. 40 μc.	6 hours	++	++	++	+	++	10 and 11
Rabbit 234 1.8 kg.	0.18 cc. 20 μc.	16 hours	+*	—*	—	—	—	12
Rabbit 233 2.8 kg.	0.2 cc. 22 μc.	24 hours	—	—	—	—	—	

+ = Presence of radioactivtiy
++, +++, and ++++ = Increasing intensity of radioactivity
— = Absence of radioactivity
* Faint radioactivity over the whole surface of the brain

bumin solution. This radioactivity is interpreted as indicating that some of the tracer became absorbed on the leptomeninges and some penetrated from the cerebrospinal fluid into the nervous tissue. Judging by the appearance of the autoradiographs, penetration took place along the broad front of the meningeal surface of the brain and along some blood vessels entering the brain tissue.

The penetration along the broad front of the brain surface was manifested by a band of diffuse radioactivity which faded gradually into the tissue depths (Figs. 4, 8, and 10). This band was broader at the base of the brain and around the transverse cerebral fissure than over the convexity of the cerebral hemispheres (Figs. 4, 6, and 10). The leptomeninges appeared as a distinct dark line (Figs. 4, 6, and 10).

Radioactivity along the blood vessels was seen in several places. The small blood vessels penetrating from the meninges into the subpial tissue were frequently radioactive. This was particularly conspicuous in the hypothalamus but was also present in the cerebral cortex (Figs. 2, 4, and 9). Several spots of radioactivity corresponding to vessels in the deeper regions of the brain were also seen (Figs. 1, 5, and 8). In the rabbit, the blood vessels in the hippocampal fissure were frequently radioactive (Fig. 11). This has not been observed in either the cat or the dog.

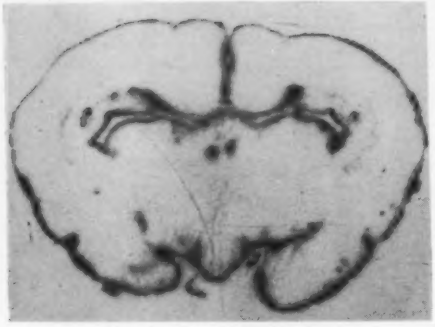


Fig. 1. (Exp. 232) Autoradiograph of a brain section taken from a rabbit that was killed twenty minutes after intracisternal injection of tracer. Moderate radioactivity is seen in the leptomeninges outlining the free surfaces of the brain, including that of the transverse fissure. Dark spots over brain tissue correspond to sites of blood vessels.

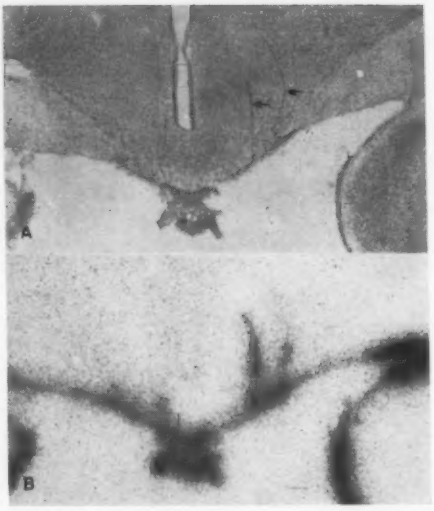


Fig. 2. (Exp. 232) [A] Photomicrograph of hypothalamus from the same brain seen in Figure 1; 2 blood vessels entering the hypothalamus from the leptomeninges are marked by arrows. [B] Corresponding autoradiograph. Note the radioactivity along the blood vessels and over the surface of the brain. No radioactivity is seen over the ependymal lining of the third ventricle.

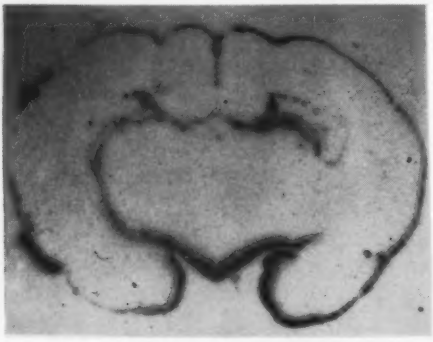


Fig. 3. (Exp. 452) Autoradiograph of a brain section taken from a rabbit that was killed one and one-half hours after intracisternal injection of tracer. Moderate radioactivity is seen in the leptomeninges and subpial brain tissue. Dark spots of radioactivity in brain tissue correspond to sites of blood vessels, as in Figure 1.

Fig. 4. (Exp. 448) Autoradiograph of a brain section taken from a rabbit that survived three hours after intracisternal injection of tracer. Note intense radioactivity in the leptomeninges and along some blood vessels penetrating the brain tissue. Radioactivity in the subpial brain tissue is more intense and occupies a broader area than it does in Figure 3.

The resolution of x-ray film emulsion does not allow a precise localization of the radioactivity in relation to the components of the vessel wall or perivascular tissue. However, we feel confident that this radioactivity was not due to blood in the lumina of the vessels because we observed that some vessels which were

radioactive did not contain blood and, on the contrary, that other vessels which contained blood were not radioactive.

The distribution of the radioactivity in the cerebellum, lower brain stem, and spinal cord deserves special description. In the cerebellum, radioactivity was present in the narrow subpial layer, but, because of the thinness of the folia, the general impression was that of a more intense darkening than in the cerebral hemispheres. In the lower brain stem, radioactivity was present beneath the pia (Fig. 7) and along the blood vessels, particularly those in the midline. In 1 dog, sections through the medulla taken at the level of the area postrema showed intense radioactivity of this structure (Fig. 7). The cervical spinal cord was investigated in 1 cat and 1 dog. The whole cross section of the cord was moderately radioactive, with more radioactivity at the periphery and slightly more in the gray matter.

A comparison of the autoradiographs obtained from animals that were killed at various intervals after injection of the tracer showed the following results. Twenty minutes after the injection, radioactivity was restricted to the leptomeninges, with only a very few streaks of darkening along the superficial blood vessels of the hypothalamus and occasional dark spots corresponding to deep vessels (Figs. 1 and 2). With a longer survival time, the darkening became more intense in the leptomeninges and along the blood vessels and appeared diffusely under the pia (Fig. 3). Radioactivity was most intense after three hours' survival time (Figs. 4 and 5), while, after six hours, the subpial band became broader but slightly less radioactive (Fig. 10). Sixteen-hour specimens showed only a faint, diffuse radioactivity over the whole brain section (Fig. 12). After twenty-four hours of survival, no radioactivity was observed in the autoradiographs.

The general pattern of the radioactivity was similar in all 3 species investigated. The only exceptions were [1] the presence of radioactivity along the blood vessels of the hippocampal fissure of the rabbit and [2] the presence of a very faint radioactivity of the ependymal lining in the dog (Figs. 8 and 9).

The difference in intensity of radioactivity seen in animals of the same species killed after the same survival time correlated well with the strength of the tracer injected (Figs. 4 and 5). Variations in the volume of the fluid injected did not seem to have an appreciable effect on the intensity and distribution of the radioactivity.

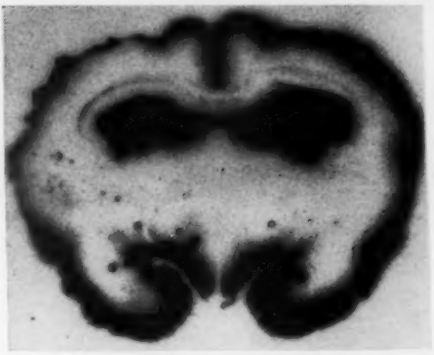


Fig. 5. (Exp. 437) Autoradiograph of a brain section taken from a rabbit that survived three hours after intracisternal injection of tracer in a dose double that used in Experiment 448. Note that the pattern of radioactivity is the same as in Figure 4 but the intensity is much greater.

Finally, we would like to mention briefly the results of two pilot experiments that we performed during the course of this investigation.

In one group of experiments, radioactive

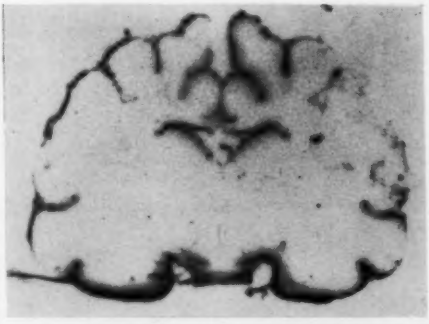


Fig. 6. (Exp. 439) Autoradiograph of a brain section taken from a cat that survived three hours after intracisternal injection of tracer. Note that the distribution of the radioactivity has the same pattern as in the previous figures but is less intense.

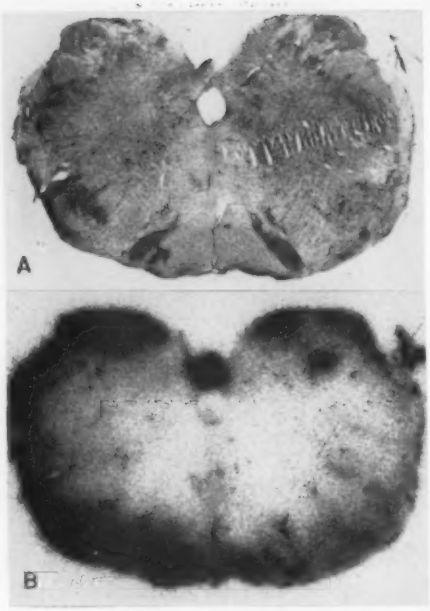


Fig. 7. (Exp. 562) [A] Photomicrograph of a section of the medulla oblongata taken from a dog that survived three hours after intracisternal injection of tracer. Note the area postrema immediately dorsal to the central canal. [B] Corresponding autoradiograph. Note the intense radioactivity corresponding to the area postrema and a band of diffuse radioactivity underneath the leptomeninges.

iodinated bovine albumin was injected into the subarachnoid space of rabbits immediately before or after the animals were killed by an overdose of Nembutal. After a few passive bending movements of the neck, the animals were left for three or six hours and the brains were then removed. In these cases, there was very intense radioactivity along the leptomeninges and also along the ependymal lining of the whole ventricular system.

In another group of experiments, the cerebrospinal fluid pressure was measured in dogs after a subarachnoid injection of various fluids. Immediately after the injection of 0.2 cc. of 2% nonradioactive bovine albumin, the cerebrospinal fluid pressure rose from 110 to 133 mm. H_2O but returned gradually to the pre-injection level within two hours. During these experiments, we observed that there was a sharp rise in cerebrospinal fluid pressure, approximately 30 to 60 mm. H_2O, if the anesthesia became lighter and the dogs started to move. This occurred even with very slight movements.

DISCUSSION

The results of our experiments indicate that molecules of albumin tagged with radioactive iodine can penetrate into the nervous tissue from the cerebrospinal fluid. We feel confident that we were observing the radioactivity of iodine still attached to the albumin and not of free, unbound ions. This confidence is based on the well-known stability of the iodine-protein bond and on the fact that, with our autoradiograph technic, unbound iodine would be washed away from the sections. We used a commercial preparation of iodinated albumin which contained about 2% of unbound iodine, and one could argue that the unbound iodine penetrated into the nervous tissue and then became attached to the tissue proteins. To answer this question, we performed a control experiment by injecting 1 μc. of radioactive

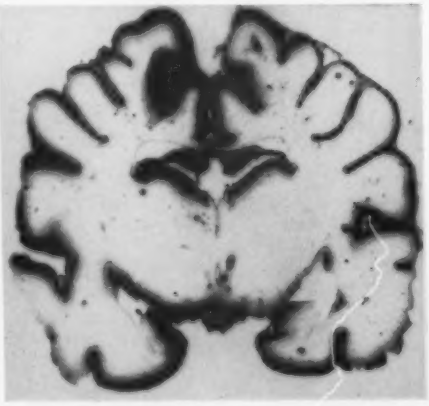


Fig. 8. (Exp. 624) Autoradiograph of a brain section taken from a dog that survived three hours after intracisternal injection of tracer. Note intense radioactivity in the leptomeninges and subpial brain tissue. Dark spots over the deep regions of the brain correspond to sites of blood vessels.

potassium iodide into the cisterna magna of a rabbit. Thus, the amount of the radioactive unbound iodine injected was 2½ times greater than that contained in 20 μc. of the iodinated albumin. Autoradiographs of brain sections from this experiment did not reveal any evidence of radioactivity.

The perivascular distribution of the radioactivity was similar to that seen by Bowsher.[2] However, in our material, we have observed radioactivity in relation to not only superficial vessels but also those deep in the brain tissue. The question arises whether this distribution occurred during life as a result of the flow of the cerebrospinal fluid or whether it was a postmortem artifact. The radioactivity in relation to the subpial blood vessels and blood vessels of the hippocampal fissure is surely not an artifact. Supporting this statement are the observations of the perivascular spread of inflammatory and neoplastic processes from the cerebrospinal fluid into the perivascular spaces of the superficial cortical vessels. Further, Iwanowski and Olszewski[8] have found that, when an iron-containing pigment was injected subarachnoidally for several weeks, the perivascular spaces of the hypothalamus and hippocampus were surrounded by an iron-containing material. Finally, the regularity with which this perivascular distribution was observed in our present investigation supports the belief that it was not an artifact. We are less sure about the origin of the radioactivity in relation to the blood vessels in the depths of the brain. It is possible that, during life, the radioactive cerebrospinal fluid moved along the perivascular space and traveled quite a distance from the pial surface. The presence of the flow of cerebrospinal fluid in these spaces has been accepted by several authors. However, although at present we are more inclined to think that we were dealing with a true physiologic phenomenon, we cannot exclude the possibility of a postmortem artifact due, for example, to a change in the volume of the brain after its fixation. Further experiments are necessary in order to settle this question.

The subpial band of diffuse radioactivity was probably caused by the penetration of tracer directly from the subarachnoidal space into the nervous tissue. Obviously, the radioactivity of the subpial tissue is not an illusion due to the scatter of radiation from the intensely radioactive meninges. The sharpness of the edge of the darkening of the emulsion at the external border of the subpial band and the gradual decrease in this darkening toward the depths of the brain are sufficient proof. Bowsher[2] has also observed slight radioactivity

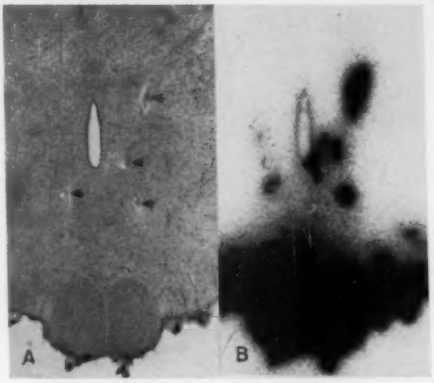


Fig. 9. (Exp. 624) Details of Figure 8. [A] Histologic section shows position of the blood vessels in the diencephalon (arrows). [B] Note the radioactivity corresponding to these vessels and to the ependymal lining of the third ventricle.

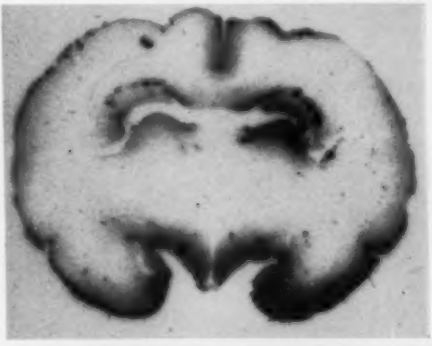


Fig. 10. (Exp. 444) Autoradiograph of a brain section taken from a rabbit that survived six hours after intracisternal injection of tracer. Pattern of the distribution of radioactivity is the same as in Figure 4, but the subpial band is broader and less dark.

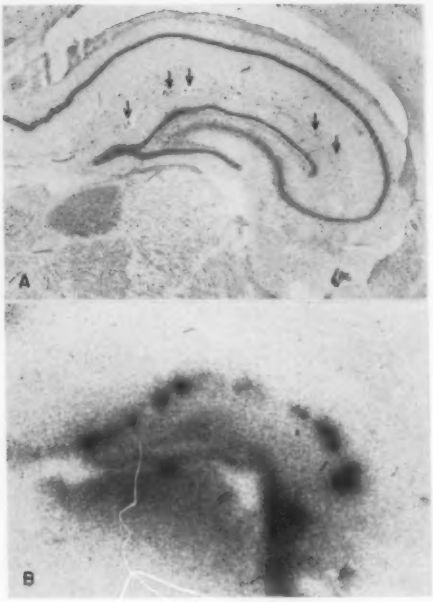


Fig. 11. (Exp. 444) Details of Figure 10. [A] Histologic section shows position of the blood vessels in the hippocampal fissure (arrows). [B] Note the radioactive spots corresponding to these vessels. Radioactivity is also present in the hippocampus and thalamus adjacent to the transverse cerebral fissure but is absent from the ependyma and subependymal tissue of the lateral ventricle.

in the subpial brain tissue after subarachnoid injection of sulphur-labeled proteins. How albumin-sized molecules penetrate through the pia-glia membrane[9] and then spread into nervous tissue reputedly devoid of extracellular spaces is difficult to understand. One of the possible ways would be by pinocytosis, and evidence exists that this phenomenon occurs in at least some cells of the nervous tissue. Thus, Klatzo[10] has seen in tissue cultures the trapping of vacuoles of the medium by the undulating astrocytic membranes.

The greater intensity of penetration into the brain tissue at the base of the brain and from the transverse cerebral fissure than at the convexity can probably be explained by the mechanics of cerebrospinal fluid circulation. In some regions, the flow may be slower because of either a "blind alley" effect or a broader channel of the given sector of the subarachnoid space. At these sites, the cerebrospinal fluid may retain a higher concentration of the tracer for a longer time. This explanation is also applicable to the high intensity of radioactivity that can be observed in the spinal cord and the periphery of the medulla.

The time at which the radioactivity disappeared from the nervous tissue after subarachnoid injection of the tracer was of approximately the same order as that previously observed by us after air embolism.[11] The 3 mechanisms that we suggested in that publication as responsible for this disappearance are also applicable to our present results. These results perhaps give certain support to the second mechanism (disappearance via the cerebrospinal fluid), since, if proteins can enter the nervous tissue from the cerebrospinal fluid, they may also be able to leave it when the gradient of concentration would favor such a movement. The investigation of Simmonds[12] and our own unpublished results indicate that such a favorable gradient may develop within ten to fifteen hours because the proteins injected subarachnoidally disappear from the cerebrospinal fluid with considerable speed. Thus, if the brain and cerebrospinal fluid are

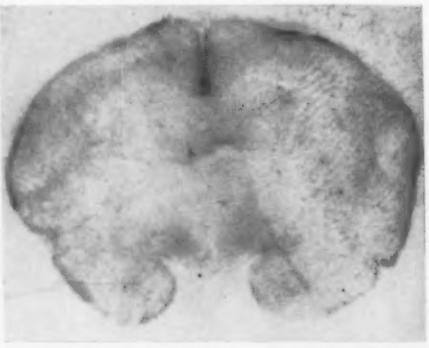


Fig. 12. (Exp. 234) Autoradiograph of a brain section taken from a rabbit that survived sixteen hours after intracisternal injection of tracer. Note only faint radioactivity over the whole surface of the section.

in some form of "equilibrium," the nervous tissue would begin losing its radioactivity as soon as the cerebrospinal fluid concentration became lower than that of the nervous tissue. It should be remembered that, in all our experiments, we have used heterologous proteins and that homologous proteins might have given somewhat different results. On the other hand, it is known that the disappearance curve of proteins introduced intravenously is identical for homologous and heterologous proteins during the first seven days after the injection, provided the animals were not previously sensitized to the heterologous proteins used.

The nearly complete absence of radioactivity in the ependymal lining and subependymal tissue is due most likely to the direction of flow of the cerebrospinal fluid. When tracer was injected into the subarachnoid space of rabbits that were killed immediately before or after the injection, the ventricular walls became intensely radioactive. In these cases, there was obviously no flow of cerebrospinal fluid and the tracer mixed with the fluid in all compartments of the ventricular system. We would like to stress that the absence of radioactivity in the ependyma of the rabbits that survived a certain time after the injection should not be understood as indicating that, under normal conditions in wakeful animals, there is no mixing of the subarachnoidal fluid with the ventricular. Under normal conditions, there must be constant fluctuation of the cerebrospinal fluid pressure resulting in temporary reversal of the direction of flow. A similar mechanism can explain Bakay's[5] results mentioned above—the presence of radioactivity in the ependyma if some cerebrospinal fluid was withdrawn before subarachnoid injection of P^{32}. We have not observed this phenomenon, but our results cannot be compared directly with Bakay's because we used a different tracer.

It can be questioned whether the penetration of proteins from the cerebrospinal fluid into the brain tissue, particularly deep perivascular penetration, was not due to an increase of cerebrospinal fluid pressure after injection of the proteins into the subarachnoid space. However, measurements of cerebrospinal fluid pressure after subarachnoid injection of a comparable amount of protein showed only a slight increase in pressure, which returned to normal within two hours. We therefore feel that the penetration we observed was not the result of an excessive rise of cerebrospinal fluid pressure. Here, we can mention again that cerebrospinal fluid pressure is not a static phenomenon but is continually changing, depending on various factors. These variations are physiologic, and their range must be higher than the slight change observed after subarachnoid injection of a small amount of proteins. Thus, if variations of cerebrospinal fluid pressure were responsible for the perivascular spread of the cerebrospinal fluid, we can expect that, in a wakeful animal or man, this spread would be even more extensive than in our anesthetized animals.

The findings reported here may be of significance in understanding the spread of pathologic processes if we accept that the pathogenic factor is present in the cerebrospinal fluid. Thus, the perivascular distribution of lesions could be due to the penetration of the agent not from the blood into the nervous tissue but from the cerebrospinal fluid along the perivascular spaces. Indeed, this route of invasion has been suggested by other authors[13] for many years, and, although our findings do not prove that such a route is significant, they support the belief that it does exist.

SUMMARY

1. Subarachnoid injections of radioactive iodinated bovine albumin were performed in rabbits, cats, and dogs.

2. An autoradiographic technic was used to study the distribution of radioactivity at various time intervals after the injections had been made.

3. Radioactivity was observed along the blood vessels in the superficial and deep regions of the brain. In addition, a broad band of diffuse radioactivity was present under the leptomeninges.

4. The peak of this radioactivity was observed three hours after an injection. After sixteen hours, the radioactivity was negligible and, after twenty-four hours, was absent.

5. These findings underline the significance of the cerebrospinal fluid as a route for the invasion of the nervous tissue in the pathogenesis of nervous diseases.

REFERENCES

1. Bakay, L.: The Blood-Brain Barrier, with Special Regard to the Use of Radioactive Isotopes. Springfield, Ill., Charles C Thomas, 1956.
2. Bowsher, D.: Pathways of absorption of protein from the cerebrospinal fluid: An autoradiographic study in the cat. Anat. Rec. 128:23, 1957.
3. Mandelstamm, M., and Krylow, L.: Vergleichende Untersuchungen ü. d. Farbenspeicherung in Zentralnervensystem bei Injectionen der Farbe ins Blut und in den Liquor Cerebrospinalis. Ztschr. f. d. ges. exper. Med. 58:256, 1928.
4. Davson, H.: Physiology of the Ocular and Cerebrospinal Fluids. London, J. & A. Churchill Ltd., 1956.
5. Bakay, L., and Lindberg, O.: Studies on the role of the cerebrospinal fluid in brain metabolism as measured with radioactive phosphate. Acta. physiol. scandinav. 17:179, 1949.
6. Selverstone, B.: Studies of the formation and absorption of the cerebrospinal fluid using radioactive isotopes. In Wolstenhome, G. E. W., and O'Connor, C. N., ed.: Ciba Foundation Symposium on the Cerebrospinal Fluid. London, J. & A. Churchill Ltd., 1958. pp. 147-164
7. Lee, J. C., and Olszewski, J.: Permeability of cerebral blood vessels in healing of brain wounds. Neurology 9:7, 1959.
8. Iwanowski, L., and Olszewski, J.: The effects of subarachnoid injections of iron-containing substances on the central nervous system. J. Neuropath. & Exper. Neurol. In press.
9. Pease, D. C., and Schultz, R. L.: Electron microscopy of rat cranial meninges. Am. J. Anat. 102:301, 1958.
10. Klatzo, I.: Personal communication.
11. Lee, J. C., and Olszewski, J.: Effect of air embolism on permeability of cerebral blood vessels. Neurology 9:619, 1959.
12. Simmonds, W. J.: The absorption of blood from the cerebrospinal fluid in animals. Australian J. Exper. Biol. & M. Sc. 30:261, 1952.
13. Uchimura, I., and Shiraki, H.: A contribution to the classification and the pathogenesis of demyelinating encephalomyelitis, with special reference to the central nervous system lesions caused by preventive inoculation against rabies. J. Neuropath. & Exper. Neurol. 16:139, 1957.

Meningeal leukemia

A syndrome resulting from increased intracranial pressure in patients with acute leukemia

Richard K. Shaw, M.D., Edward W. Moore, M.D.,
Emil J. Freireich, M.D., and Louis B. Thomas, M.D.

AN INCREASING NUMBER of patients with acute leukemia who have clinical evidence of meningeal irritation and increased intracranial pressure, unrelated to hemorrhage or infection, are now being observed. This syndrome, which we shall term meningeal leukemia, is related to infiltration of the arachnoid by leukemic cells.[1] Meningeal leukemia is of considerable interest because it may be the only initial evidence of acute leukemia, may appear in patients who are in hematologic remission, is often a difficult diagnostic problem, is associated with a high patient morbidity, and may be a direct cause of death. The purpose of this paper is to define in detail the clinical manifestations of meningeal leukemia which have been noted in 25 (16.7%) of 150 patients with acute leukemia admitted consecutively to our center. A review of the medical literature on meningeal involvement in leukemia will be presented and considered in relation to our findings.

PATIENT MATERIAL AND METHODS

The medical records of the first 150 patients with acute leukemia admitted to the Clinical Center from July 1, 1953, to April 1, 1958, were reviewed. The patients are classified by cell type, age, and sex in Table 1. The age range was 4 months to 78 years. The predominance of lymphocytic leukemia in children and myelocytic leukemia in adults is in accord with previous reports.[2] However, the marked male predominance in both age groups is somewhat greater than has previously been described. All but 15 of these patients had been cared for during life by at least one of the authors.

Neurologic signs and symptoms ascribable only to meningeal leukemia were found in 25 patients. Patients with intracranial hemorrhage, central nervous system infections, isolated spinal cord involvement, peripheral neuropathy, or drug toxicity were not included in the meningeal leukemia group. If data were insufficient to exclude other causes, patients who had neurologic changes that may have been due to leukemic infiltration of the meninges were also not included in the meningeal leukemia group. Of the 25 patients with meningeal leukemia, 6 have been briefly described in a previous publication.[3]

Of the 150 patients, 141 had died by the time of the study. The central nervous system was examined at autopsy in 117 of these. Of the 25 patients with meningeal leukemia, 2 were living at the time of this report; pathologic examination of the central nervous system was performed in all of the other 23.

The diagnosis of acute leukemia was established in each patient by bone marrow examination. Antileukemic therapy, consisting of 6-mercaptopurine (6-MP), Methotrexate, adrenal steroids, and experimental drugs, was handled in a uniform manner under the study programs of the Acute Leukemia Cooperative Group B.[4,5] The criteria for hematologic remission and relapse were those published by the Clinical Studies Panel of the Chemotherapy National Service Center.[6] Analysis of the data was made by the chi square test.[7] Life tables were constructed by the standard technic.[8] Radiation therapy doses given in the text refer to tissue doses.

From the National Cancer Institute and the Department of Pathologic Anatomy, Clinical Center, National Institutes of Health, Bethesda, Md.
Dr. Shaw's present address is the Department of Medicine, University of Washington Medical School, Seattle. Dr. Moore is now with the Second and Fourth (Harvard) Medical Services, Boston City Hospital.

TABLE 1

CLASSIFICATION OF 150 PATIENTS WITH ACUTE LEUKEMIA BY CELL TYPE,* AGE,† AND SEX

Cell type	Number of patients	Sex	
		Male	Female
Lymphocytic	93(62%)	58	35
Children	63	43	20
Adults	30	15	15
Myelogenous	57(38%)	38	19
Children	6	4	2
Adults	51	34	17
Total	150	96	54

*4 patients with acute monocytic leukemia are classified as myelogenous.
†Patients less than 15 years of age at the time of admission to the Clinical Center are classified as children.

TABLE 2

CLASSIFICATION OF 25 PATIENTS WITH MENINGEAL LEUKEMIA

Cell type	Number of patients	Sex	
		Male	Female
Lymphocytic	23	20	3
Children	21	19	2
Adults	2	1	1
Myelogenous	2	2	0
Children	1	1	0
Adults	1	1	0
Total	25	22	3

TABLE 3

MAJOR SYMPTOMS OF MENINGEAL LEUKEMIA

Symptom	Number of patients	Per cent
Nausea and anorexia	23	92
Lethargy	22	88
Vomiting	21	84
Headache*	14	56
Convulsions†	14	56
Coma	11	44
Visual change	11	44

*Could not be evaluated in 8 patients
†Status epilepticus in 2 patients

TABLE 4

MAJOR SIGNS OF MENINGEAL LEUKEMIA

Sign	Number of patients	Per cent
Papilledema	16	64
Tendon reflex changes	10	40
Facial nerve palsy	9	36
Positive Babinski	8	32
Nuchal rigidity	7	28
Pupillary changes	5	20
Abducens nerve palsy	4	16

RESULTS

Clinical and laboratory data. The 25 patients with meningeal leukemia are classified by age, sex, and morphologic type of leukemia in Table 2. The majority of the patients were male children with lymphocytic leukemia. To determine the significance of this distribution, the frequency of meningeal leukemia was analyzed in the total population of 150 patients (Fig. 1). The syndrome was found to occur primarily in children with lymphocytic leukemia and was more frequent in males than females.

The principal clinical findings in the 25 patients with meningeal leukemia are recorded in Tables 3 and 4. Persistent nausea and vomiting were the most common symptoms and were often initially interpreted as antimetabolite toxicity. Headaches were often severe, requiring narcotics for relief. In 8 young children, it was impossible to ascertain whether headaches were present. Unexplained lethargy with episodic irritability was a common early observation. Grand mal seizures, coma, and visual difficulties such as blurring and diplopia were often present. Numerous other neurologic symptoms such as ataxia, vertigo, and tinnitus occurred in an occasional patient. A 5-year-old boy with acute leukemia had marked hyperphagia, obesity, and destructive behavioral disturbances. The most frequent sign of meningeal leukemia was papilledema (Table 4). However, symptoms of increased intracranial pressure often preceded this finding by weeks. Abnormalities of the deep tendon reflexes were common, and diffuse muscular weakness was also frequently observed; 2 patients became paraplegic. Sensory deficits were rare. Cranial nerve involvement was common. In addition to facial and abducens nerve palsies, unilateral oculomotor nerve palsies occurred in 2 patients, and, in three patients, blindness developed after longstanding papilledema. Partial deafness was found in 2 patients. Nuchal rigidity was infrequent and, when present, was mild. A positive Kernig's sign was noted in only 1 patient.

Of the 25 patients with meningeal leukemia, 20 had a total of 59 examinations of the cerebrospinal fluid. Pressure greater than 150 mm. of water was present in 16 of the 18 patients in whom the measurement was made; 9 pa-

tients had pressures above 250 mm. of water, and 2 had pressures exceeding the limits of the manometer (600 mm.). Pleocytosis of mononuclear cells, predominantly lymphocytes, was found in 16 of the patients. The cell counts ranged from 26 to 11,000 per cubic millimeter. Examination of fresh preparations under the phase microscope in many instances permitted identification of the cells as abnormal, leukemic "blasts." However, morphologic detail was not well preserved, and, frequently, the cells could only be classified as lymphocytes. No correlation existed between the cerebrospinal fluid white counts and the peripheral blood leukocyte counts. Protein levels exceeded 45 mg. per cent in 4 cases, the highest value being 372 mg. per cent. Blood sugar concentrations in 2 patients were 81 mg. per cent and 70 mg. per cent, while spinal fluid sugar concentrations (Nelson-Somogyi) were 9 mg. per cent and 25 mg. per cent, respectively; 4 more individuals had cerebrospinal fluid sugar levels between 40 to 50 mg. per cent, but these were considered normal because concomitant blood sugar determinations were not made. Routine bacteriologic cultures of the cerebrospinal fluid were performed on 18 patients and were all negative. Special cultures for viruses were done in 7 patients, for tuberculosis in 4, and for fungi in 2; all of these were also negative. The cerebrospinal fluid of every patient examined demonstrated either increased pressure or an increased white cell count; 2 patients had pleocytosis without increased pressure, and 4 had only increased pressure. The remaining 14 patients had increases in both the pressure and cell count. Lumbar punctures were performed in 11 patients with acute leukemia who did not have meningeal leukemia. In all 11, the cerebrospinal fluid determinations were normal. Although several patients with increased pressure had multiple lumbar punctures, no complications were encountered. On 15 occasions, lumbar punctures were performed when the platelet counts were less than 10,000 per cubic millimeter but no bleeding problems developed.

All patients had skull roentgenograms taken. The most frequent abnormality found in the patients with meningeal leukemia was widened cranial sutures, which was seen in 16 of the

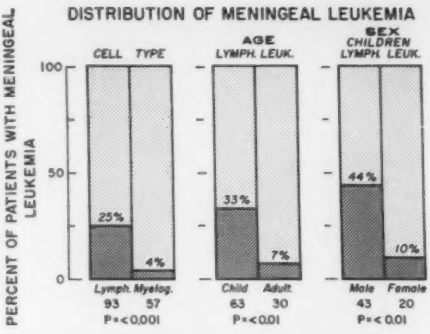


Fig. 1. All 150 patients were considered under cell type. Only the 93 patients with lymphocytic leukemia were analyzed for age, and only the 63 children with lymphocytic leukemia were analyzed for the sex distribution of meningeal leukemia.

17 children below age 11. None of the 8 patients over age 11 had spread sutures. All major cranial sutures were usually involved, and, less frequently, recognized ones such as the sphenooccipital and squamoparietal were involved (Fig. 2). Increased digital markings were observed in 3 patients, 2 of whom did not have spread suture lines (Fig. 3). One adult had local erosion of the lesser wing of the sphenoid. Thinning of the dorsum sellae

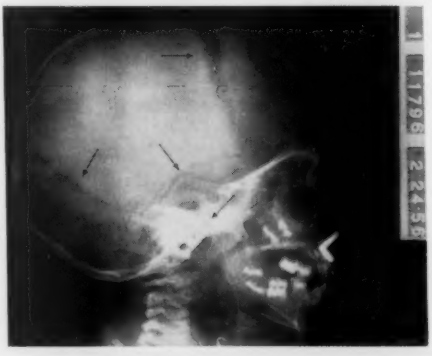


Fig. 2. Lateral skull roentgenogram taken soon after clinical onset of meningeal leukemia. Widening of the coronal, lambdoidal, squamoparietal, and sphenooccipital sutures is present.

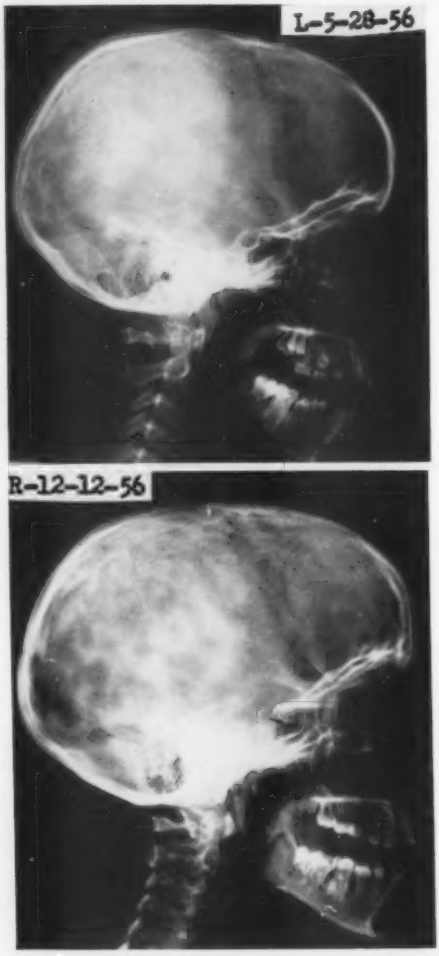


Fig. 3. Lateral skull roentgenograms taken *(top)* on admission to the hospital (May 28, 1956) and *(bottom)* two weeks before death (December 12, 1956). The digital markings are increased, and the dorsum sellae is thinned, without spread suture lines.

was present in 2 children. No radiologic changes were found in 6 patients with meningeal leukemia. The observation of spread suture lines on a routine skull roentgenogram was the initial objective evidence of meningeal leukemia in 5 patients.

Electroencephalograms were made in 21 of the 25 patients; 2 could not be evaluated because the patients were receiving 6-azauracil therapy, which is known to produce electroencephalographic changes.[9] Of the remaining 19 patients, 17 had diffuse dysrhythmias and 2 had focal abnormalities. The diffuse patterns were nonspecific theta and delta wave activity. The focal changes were also nonspecific.

Relationship between meningeal leukemia and systemic acute leukemia. Meningeal leukemia was found to occur at any stage of the clinical course of acute leukemia: as an initial manifestation, during an active phase after chemotherapy, and during complete or partial hematologic remission. Evidence of meningeal leukemia was noted in 4 patients upon admission, before any therapy; 13 patients who had been treated previously were in an active hematologic phase of the disease. Of the remaining 8 patients, 4 were in unequivocal complete hematologic remission with normal physical examinations, peripheral blood counts, and bone marrow aspirations. They remained in complete hematologic remission for three weeks, seven weeks, three months, and five months, respectively, while the meningeal leukemia persisted. Another 2 patients were in either partial or complete hematologic remission at the onset of the neurologic syndrome. They had normal physical examinations and peripheral blood counts, but bone marrow aspiration was not performed. In both, bone marrow findings revealed relapse within two to three weeks after the appearance of meningeal leukemia. The seventh patient had normal physical findings and peripheral blood counts but only a partial remission by bone marrow aspiration. Relapse occurred in two weeks. The last patient had a normal bone marrow when meningeal leukemia, leukemia cutis, and leukemic lymphadenopathy were present. Hematologic relapse followed in two weeks.

The 8 patients who were in either partial or complete hematologic remission when meningeal leukemia appeared were all receiving antimetabolite therapy; 5 were receiving 6-MP and 3 were receiving 6-MP and Methotrexate. Thus, meningeal leukemia may develop during the daily administration of antimetabolites that successfully maintain a hematologic remission.

Since 21 of the 25 patients with meningeal leukemia were children with lymphocytic leukemia, these children were compared with the 42 children with lymphocytic leukemia who did not have meningeal involvement. The former had a slightly shorter life span than the latter (Fig. 4). Life table comparisons of only the male children with and without meningeal leukemia, from the time of diagnosis of leukemia or from admission to the hospital, showed essentially the same curves. Moreover, the frequency and extent of response to systemic chemotherapy was similar for children with and without meningeal leukemia.

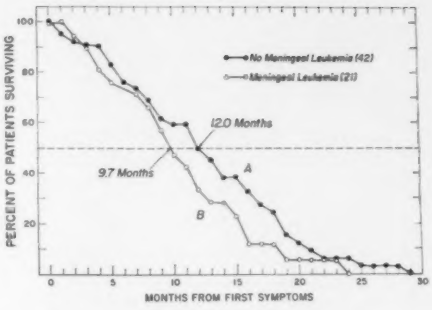


Fig. 4. Survival of 63 children with acute lymphocytic leukemia. The 12.0 and 9.7 months figures are the 50% survival times for each group.

For the 21 children with lymphocytic leukemia who had meningeal leukemia, the median time from the symptomatic onset of systemic leukemia to the onset of the meningeal syndrome was seven months, with a range of zero to nineteen months. The number of new cases of meningeal leukemia occurring during each month of the disease course was approximately the same. The median survival after onset of meningeal leukemia in the children with lymphocytic leukemia was three months, with a range of one-half to eleven months. This indicated that the appearance of meningeal leukemia was a poor prognostic sign. The survival from the onset of meningeal leukemia in our 25 patients has been compared to the survival from relapse after remission in 14 patients (12 children and 2 adults) with acute leukemia who relapsed from remission on combination 6-MP and Methotrexate therapy[4] (Fig. 5). The 2 life table curves are very similar, suggesting that the appearance of meningeal leukemia has a prognostic significance similar to that of relapse from remission.

Meningeal leukemia per se was seldom a cause of death. Only 2 of the patients died as a direct result of increased intracranial pressure; 2 of the 23 patients had terminal intracranial hemorrhages, and 2 died with bacterial meningitis.

Response of meningeal leukemia to treatment. All 25 patients received antileukemic chemotherapy after the development of meningeal leukemia; 17 had no further hematologic remissions, while the remaining 8 experienced 2 complete and 7 partial remissions. Concomitant neurologic improvement uncomplicated by whole brain irradiation or intrathecal Methotrexate occurred in 6 of these 8 patients (Fig. 6). However, of the 17 patients who failed to achieve another remission, only 2 demonstrated neurologic improvement, which in both was of short duration. Neurologic improvement with systemic chemotherapy occurs primarily when a systemic remission occurs ($P = <0.01$). To evaluate which drugs were effective in the management of meningeal leukemia, only those compounds which had not previously been administered to a patient were

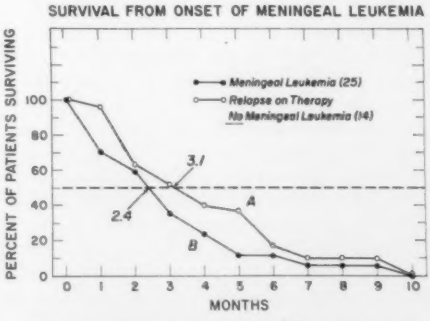


Fig. 5. Curve A is the life table of 14 patients who relapsed from remission on combination 6-MP and Methotrexate therapy and starts at the time of relapse. Curve B is the life table of the 25 patients with meningeal leukemia and starts at the time of diagnosis of meningeal leukemia (B). The 3.1 and 2.4 months figures are the respective 50% survival times for each group.

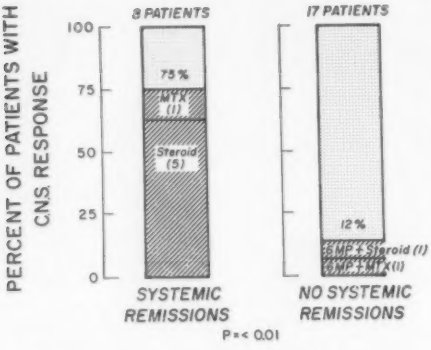


Fig. 6. Effect of systemic chemotherapy on meningeal leukemia. Systemic remission means either a partial or complete hematologic remission.

considered. Trials of antimetabolites given were Methotrexate, 8; 6-MP, 3; and combination 6-MP and Methotrexate, 1; 2 (17%) of the 12 trials resulted in an improvement of the meningeal leukemia, 1 with Methotrexate and 1 with combination therapy. However, in neither patient was this sustained neurologic remission. Of the 8 trials of corticosteroids, 5 resulted in both hematologic remissions and sustained neurologic improvement. Clinical "cures" of meningeal leukemia were obtained with adrenal steroids in 2 patients. The difference in the incidence of central nervous system response to antimetabolites and steroids is not statistically significant ($P = 0.14$). However, the neurologic remissions with corticosteroids were more frequent and more complete than those obtained with antimetabolites.

Whole brain radiation therapy was administered to 7 patients with meningeal leukemia. The dosage utilized was from 600 to 1,000 r over eight to thirteen days; 3 patients had good responses lasting two to three months, but 1 child improved for only one month. The response to whole brain irradiation in the remaining 3 patients could not be evaluated because they died within two weeks after completion of therapy. Local radiation therapy was given to 3 other patients for cranial nerve involvement; 2 had good sustained responses, but the third died eight days after therapy and could not be evaluated. The patients tolerated the irradiation well, and the only side effect of note was temporary alopecia.

Intrathecal Methotrexate in single doses of 2.5 mg. (0.2 mg. per kilogram), 2.6 mg. (0.4 mg. per kilogram), 5 mg. (0.2 mg. per kilogram), and 13 mg. (0.4 mg. per kilogram) was given to 4 patients with meningeal leukemia; 3 had definite neurologic improvement, while the fourth died soon after treatment. The responses were very prompt with improvement evident within one to two days, but remissions lasted only three to six weeks.

The evolution of meningeal leukemia and its response to therapy can be evaluated by periodic examination of the cerebrospinal fluid, electroencephalograms, and skull roentgenograms. In each of these parameters, return toward normal has been observed concomitant with clinical remission of meningeal leukemia.

DISCUSSION

The clinical syndrome of meningeal leukemia has increased in importance since the advent of effective antileukemic therapy. We have found 100 patients with the syndrome of meningeal leukemia reported before April 1959.[10-61] These patients are classified in Table 5. Over the seventy-year period before the availability of antileukemic chemotherapy (1878-1948), only 31 patients with this syn-

TABLE 5
CLASSIFICATION OF 100 PATIENTS WITH MENINGEAL LEUKEMIA REPORTED IN THE LITERATURE

Classification	*No chemotherapy**	*Chemotherapy†*	*Total*
Age			
Adults	23	6	29
Children	8	63	71
Sex			
Male	19	43	62
Female	11	24	35
Not stated	1	2	3
Type			
Acute lymphocytic	10	49	59
Acute "stem"	7	12	19
Acute myelogenous	6	5	11
Acute monocytic	1	2	3
Chronic lymphocytic	1	0	1
Chronic myelogenous	3	0	3
Uncertain	3	1	4

*Patients who had meningeal leukemia after 1948 but who did not receive chemotherapy are classified under no chemotherapy.
†Chemotherapy refers to folic acid antagonists, 6-mercaptopurine, and corticosteroids or ACTH.

drome were reported. In contrast, during the ten-year period after the introduction of chemotherapy (1949-1959), 69 patients have been reported. It is apparent that the syndrome is being reported more often and probably is occurring more often. In patients who did not receive chemotherapy, meningeal leukemia was reported more frequently in adults, while, in patients who received chemotherapy, the syndrome was described predominantly in children. Thus, the increase of meningeal leukemia has occurred primarily in children, who as a group respond better to antileukemic therapy than do adults.[4,5,62] Before chemotherapy, the median life span of children with acute leukemia was three to four months, but this has now increased to about twelve months in both our group (Fig. 4) and others.[62,63] Of our 21 children with meningeal leukemia, only 8 had the meningeal syndrome within four months of onset of leukemia. It would seem that the prolonged survival of children with acute leukemia is at least in part responsible for the increased recognition of the syndrome of meningeal leukemia.

Approximately one-third of our patients were in hematologic remission at the onset of signs and symptoms of meningeal leukemia. By including our 8 patients, we have been able to compile 44 case histories of meningeal leukemia occurring during partial or complete hematologic remission.[38–43, 50–53, 57–61] The majority of these patients were on antimetabolite therapy at this time. Although there are insufficient data now available, the studies which have so far been conducted on the cerebrospinal fluid concentrations of 6-MP and the folic acid antagonists indicate poor crossing of the "blood-brain barrier" by these antimetabolites, particularly the latter, when they are administered by the conventional daily oral schedule.[39,58,64,65] Further pharmacologic investigations on the crossing of the "blood-brain barrier" by these compounds must be performed before any definite conclusions can be reached, but it now appears that the failure of these agents to traverse this barrier may play a role in the development of meningeal leukemia.

Meningeal leukemia occurs predominantly in patients with lymphocytic leukemia (Tables 2 and 5). Other lymphocytic lymphomas not associated with leukemia can produce neurologic complications. While the majority of these complications result from spinal cord or nerve root compression by epidural tumors, 16 descriptions of a clinical syndrome similar to meningeal leukemia have been found.[24,58,66–75]

The pathogenesis of meningeal leukemia relates to a diffuse leukemic cell infiltration of the arachnoid.[1] The infiltration results in increased fluid pressure and hydrocephalus involving all 4 ventricles symmetrically, apparently by interfering with the flow of cerebrospinal fluid. The neurologic abnormalities found in patients with meningeal leukemia are primarily a result of the increased cerebrospinal fluid pressure. On examination of the spinal fluid, specimens from virtually all of the patients show increased pressure and pleocytosis of leukemic cells. The low cerebrospinal fluid sugar levels observed in patients with meningeal leukemia may result from increased glycolysis by the leukemic cells. A decrease in the cerebrospinal fluid sugar level after in vitro incubation with leukemic cells has been described in 2 separate reports.[28,52] However, Goldring and Harford[76] suggest that alterations in the "blood-brain barrier" may decrease the diffusion of glucose across this membrane and result in low cerebrospinal fluid sugar levels.

The characteristic radiologic finding in patients with meningeal leukemia is spreading of the cranial sutures. Because of the anatomic fusion of the suture lines which occurs during adolescence, this feature is rarely seen in adults.[77] The importance of skull roentgenograms is illustrated by the fact that, in 5 of our children, spread suture lines appeared before any definite clinical changes indicative of increased intracranial pressure were noted. Hitzig and Siebenmann[78] have reported 2 children with acute leukemia and spread cranial suture lines. They attributed this finding to leukemic infiltration of the suture lines. We have examined microscopically the suture lines in a patient who demonstrated radiographic separation during life; no infiltrations were found. Moreover, the rapidity with which suture dehiscence develops and its excellent correlation with papilledema and increased spinal fluid pressure in our series and others[53,60] suggest that spreading of the suture lines in patients with meningeal leukemia also results pri-

marily from elevation of the cerebrospinal fluid pressure.

The patient who had striking hyperphagia, pathologic weight gain, and behavioral disturbances was found at necropsy to have massive leukemic infiltration of the hypothalamus. Since 1954, 12 other cases of hyperphagia and marked obesity in association with meningeal leukemia have been described.[37,38,42,43,53,56,59–61] These patients, as well as our patient, had received chemotherapy, but only 5 had received corticosteroids when the obesity began to appear. Thus, it is not possible to incriminate corticosteroid therapy in the etiology of this syndrome; 4 of the patients had normal urinary 17-ketosteroid determinations. In 6 of the 12 previous cases, autopsies were performed, and hypothalamic and/or pituitary infiltration was found in each instance. Thus, meningeal leukemia may be associated with a "hypothalamic syndrome" that is most likely due to leukemic infiltration of this area. Finally, 2 cases of diabetes insipidus, apparently related to infiltration of the posterior pituitary and/or hypothalamus, have also been reported.[48,49]

Meningeal leukemia must be differentiated from other disorders that cause gastrointestinal or central nervous system symptoms. The nausea and vomiting resulting from meningeal leukemia may be incorrectly attributed to antimetabolite toxicity, while the meningeal signs may be attributed to meningitis, hemorrhage, or tumor. For patients known to have acute leukemia, meningeal leukemia is presently the commonest cause of meningeal signs and increased intracranial pressure. However, meningeal leukemia may be the presenting symptom of acute leukemia. Including our 4, 33 patients have now been described who presented with neurologic signs as the first evidence of leukemia,[11-14,21-35,44-47,54,60] and 8 of these 33 had no hematologic evidence of leukemia for several weeks to months after hospitalization. The diagnosis of meningeal leukemia is confirmed by the cerebrospinal fluid findings of increased pressure, pleocytosis of leukemic cells, and negative cultures.

Systemic chemotherapy, whole brain irradiation, and intrathecal Methotrexate are now being used in the treatment of meningeal leukemia. Systemic chemotherapy may be beneficial if a hematologic remission develops (Fig. 6). Although antimetabolites may improve the neurologic status of an occasional patient, these compounds, in general, are not effective in the management of this disorder. We have been impressed with the improvement of meningeal leukemia when corticosteroids are used. Sullivan[53] has also commented on the favorable responses to corticosteroids. We have been unable to find any direct measurement of corticoid levels in the cerebrospinal fluid. However, the fact that corticosteroids are able to resolve the leptomeningeal inflammation of tuberculous meningitis[79] and talc-induced reactions[80] provides indirect evidence that they do reach this area. Adrenal corticoids are easily administered and provide a prompt neurologic improvement when one occurs. Whole brain irradiation is an effective and easy means of treating meningeal leukemia. Using 500 to 1,000 r doses, improvement occurs in about 75% of patients, with beneficial effects usually apparent in two weeks.[53] Recurrences of meningeal leukemia may sometimes be successfully managed by a second course of whole brain irradiation, but resistance often appears.[58] Pathologic studies have shown that meningeal infiltrations occur around the spinal cord as well as the brain.[1] Whole brain irradiation may spare the leukemic cells along the spinal cord, which may then repopulate the central meninges. Irradiation of both the brain and cord has not been attempted to our knowledge, but it is a potentially hazardous undertaking because of severe bone marrow depression which may follow. In addition, temporary alopecia is an undesirable side effect of whole brain irradiation. Intrathecal Methotrexate is an effective means of treating meningeal leukemia and may be beneficial in the face of hematologic Methotrexate resistance. Intrathecal Methotrexate is easily administered, does not produce untoward neurologic side effects, and is very prompt in its action. Other authors[58–60] have also observed good improvements in meningeal leukemia with this technic. The beneficial effects last about four to six weeks. In an individual with meningeal leukemia, the following treatment program now seems logical:

A four-week course of corticosteroids in high doses should be the initial choice, if they have not been previously administered. Should fur-

ther therapy be necessary, whole brain irradiation or intrathecal Methotrexate may next be employed. Intrathecal hydrocortisone has been used in patients with multiple sclerosis[81] and in one child with meningeal leukemia.[50] This route of administration might be more effective in the management of meningeal leukemia. No reports are available on the use of intrathecal 6-MP, which might also be of potential benefit.

SUMMARY

Meningeal leukemia is a clinical syndrome resulting from increased intracranial pressure in patients with acute leukemia. This syndrome has been noted in 25 (16.7%) of 150 patients with acute leukemia admitted consecutively to our service. The clinical syndrome consists of nausea and vomiting, lethargy, headaches, convulsions, papilledema, cranial nerve palsies, and nonspecific neurologic signs. The skull suture lines are usually spread in children, and the electroencephalogram shows diffuse theta and delta wave activity. The spinal fluid demonstrates increased pressure, pleocytosis of leukemic cells, and negative cultures. Elevated protein concentrations and decreased sugar concentrations may also be found in the cerebrospinal fluid.

Any patient with acute leukemia may have this syndrome, but it is primarily a complication of acute lymphocytic leukemia in children. Meningeal leukemia may occur at any stage of the disease: as an initial manifestation, during hematologic remission, or during an active leukemic phase; 8 of our patients were in hematologic remission when this syndrome developed. Although meningeal leukemia is seldom fatal, it is associated with a high morbidity. The life span of children with meningeal leukemia is slightly shorter than that of children without this complication. The appearance of meningeal leukemia is a poor prognostic sign and is indicative of relapse, regardless of the hematologic status.

Meningeal leukemia is occurring more frequently since the advent of antileukemic therapy. This increase is in part related to the ability of the antimetabolite to prolong the life span of patients, particularly children, with acute leukemia. It is possible that the failure of the antimetabolites to cross the "blood-brain barrier" may also play a role in the genesis of meningeal leukemia.

Meningeal leukemia may be treated with adrenal steroids administered systemically, whole brain irradiation, or intrathecal Methotrexate. The advantages and hazards of these forms of therapy are discussed.

Several staff members of the National Institute of Neurological Diseases and Blindness, particularly Dr. Gunter Haase, assisted us with consultations. Dr. George Brecher examined the bone marrow aspirations and aided with the supravital microscopy of the spinal fluid. Dr. Theodore Hilbish and Dr. Kristoff Abraham, respectively, reviewed the skull roentgenograms and the electroencephalograms with us. Miss Joan Gurian performed the statistical analyses. Dr. Emil Frei III and Dr. Charles G. Zubrod offered helpful suggestions during the preparation of this manuscript.

REFERENCES

1. Moore, E. W., Thomas, L. B., Shaw, R. K., and Freireich, E. J.: The central nervous system in acute leukemia: A postmortem study of 117 consecutive cases with particular reference to hemorrhage, leukemic infiltrations and the syndrome of meningeal leukemia. Arch. Int. Med. 105:451, 1960.
2. Tivey, H.: The natural history of untreated acute leukemia. Ann. New York Acad. Sc. 60:322, 1954.
3. Wells, C. E., and Silver, R. T.: The neurologic manifestations of the acute leukemias: A clinical study. Ann. Int. Med. 46:439, 1957.
4. Frei, E., III, Holland, J. F., Schneideran, M. A., Pinkel, D., Selkirk, G., Freireich, E. J., Silver, R. T., Gold, G. L., and Regelson, W.: A comparative study of two regimens of combination therapy in acute leukemia. Blood 13:1126, 1958.
5. Frei, E., III, and Haurani, F.: A comparative study of three antimetabolite regimens in the treatment of acute leukemia. Proc. Am. Assn. Cancer Res. 3:20, 1959.
6. Bisel, H. F.: Letter to the editor. Blood 11:676, 1956.
7. Eisenhart, C., Hastay, M. W., and Wallis, W. A.: Techniques of Statistical Analysis. New York, McGraw-Hill Book Co., 1947.
8. Dublin, L. I., Lotka, A. J., and Spiegelman, M.: Length of Life. 2d ed. New York, Ronald Press Co., 1949.
9. Wells, C. E., Ajmone-Marsan, C., Frei, E., III, Tuohy, J. H., and Shnider, B. I.: Electroencephalographic and neurological changes induced in man by the administration of 1,2,4, triazine-3,5 (2H, 4H)-dione (6-azauracil). Electroencephalog. & Clin. Neurophysiol. 9:325, 1957.
10. Eisenlohr, C.: Leucaemia lienalis, lymphatica et medullaris, mit multiplen Gehirnnervenlähmungen. Virchows Arch. f. path. Anat. 73:56, 1878.
11. Friedlander, C.: Ein Fall von multiplen leukämischen Neubildungen des Gehirns und der Retina mit

den klinischen Erscheinungen eines Hirntoumors. Virchows Arch. f. path. Anat. 78:362, 1879.
12. Kast, A.: Beiträge zur Pathologie der Leukämie. Ztschr. f. klin. Med. 28:79, 1895.
13. Alt, F.: Ein Fall von Morbus Ménière bedingt durch leukämische Erkrankung des Nervus acusticus. Wien. klin. Wchnschr. 21:849, 1896.
14. Munro, E. E. H.: Acute myeloid leukemia simulating meningitis. J.A.M.A. 74:603, 1920.
15. Kambe, T.: Ueber Stauungspapille bei Leukämie und Gelbfärbung des Augenhintergrundes durch ein Lymphom der Chorioidea. Klin. Monatsbl. f. Augenh. 52:79, 1914.
16. Barker, L. F.: Neutrophilic myelocytes in cerebrospinal fluid of a patient suffering from myeloid leukemia and their significance for the diagnosis of myeloleukemic infiltration of the leptomeninges. South. M. J. 14:437, 1921.
17. Bass, M. H.: Leukemia in children, with special reference to lesions in the nervous system. Am. J. M. Sc. 162:647, 1921.
18. Holmes, G.: Discussion on disorders of the blood and their ophthalmological manifestations. Tr. Ophth. Soc. U. Kingdom 43:161, 1923.
19. Tromner, E., and Wohlwill, F.: Ueber Erkrankungen des Nervensystems, insbesondere der Hirnnerven bei Leukämie. Deutsche Ztschr. f. Nervenh. 100:233, 1927.
20. Sparensburg, J. J.: Leucemia linfógena aguda a iniciación visceral poco frecuente, presentando además una diplegia facial y la parálisis del motor ocular externo izquierdo. Prensa méd. argent. 15:329, 1928.
21. Winkler, W.: Ueber neurologische Symptome bei Leukämie mit einem Beitrage zur symptomatischen Aleukie. Ztschr. f. d. ges. Neurol. u. Psychiat. 137: 385, 1931.
22. Howell, A., and Gough, J.: Acute lymphatic leukemia with facial diplegia and double abducens palsy. Lancet 222:723, 1932.
23. Hill, E.: Papilledema and intracranial complications of leukemia. Am. J. Ophth. 15:1127, 1932.
24. Viets, H. R., and Hunter, F. T.: Lymphoblastomatous involvement of the nervous system. Arch. Neurol. & Psychiat. 29:1246, 1933.
25. Cooke, J. V.: Acute leukemia in children. J.A.M.A. 101:432, 1933.
26. Garvey, P. H., and Lawrence, J. S.: Facial diplegia in lymphatic leukemia. J.A.M.A. 101:1941, 1933.
27. Diamond, I. B.: Leukemic changes in the brain. Arch. Neurol. & Psychiat. 32:118, 1934.
28. Schwab, R. S., and Weiss, S.: The neurologic aspect of leukemia. Am. J. M. Sc. 189:766, 1935.
29. Murphy, J. P., and Brody, B. S.: Nerve root infiltration in myelogenous leukemia. J.A.M.A. 115: 1544, 1940.
30. Hansen, E. W.: Eye lesions in leukemia. Minnesota Med. 25:580, 1942.
31. Lipton, B. S., and Bucy, P. C.: Aleukemic leukemia with involvement of the central nervous system. J. Nerv. & Ment. Dis. 107:480, 1948.
32. Gelin, G., and Rosan, H.: Leucose aiguë avec leucoblastorachie et syndrome méningé. Rôle eventuel de la grossesse. Bull. et mém. Soc. méd. hôp. Paris 67: 633, 1951.
33. Oulie, C.: Ascenderende polyradiculitt ved akutt leukemi. Nord. med. 49:645, 1953.
34. Creakoff, A. J.: Leukemia: oddities in onset and course. M. Clin. North America 37:1747, 1953.
35. Miner, P. F., and Parks, E. W.: Transverse myelitis in lymphosarcoma. Rocky Mountain M. J. 51:41, 1954.
36. Poncher, H. G., Waisman, H. A., Richmond, J. B., Horak, O. A., and Limarzi, L. R.: Treatment of acute leukemia in children with and without folic acid antagonists. J. Pediat. 41:377, 1952.
37. Oehme, J. V.: Wandlung des Erscheinungsbildes kindlicher Leukosen unter ACTH-Behandlung. Deutsche med. Wchnschr. 79:921, 1954.
38. Sansone, G.: Pathomorphosis of acute infantile leukemia treated with modern therapeutic agents; "meningoleukaemia" and Frölich's obesity. Ann. paediat. 183:33, 1954.
39. Hamilton, L., and Elion, G. B.: Fate of 6-mercaptopurine in man. Ann. New York Acad. Sc. 60:304, 1954.
40. Pierce, M.: Leukemia in children: Treatment of 22 cases with 6-mercaptopurine. Ann. New York Acad. Sc. 60:415, 1954.
41. Bernard, J., and Seligmann, M.: A study of 61 leukemias treated with 6-mercaptopurine. Ann. New York Acad. Sc. 60:385, 1954.
42. De Toni: Aussprache. Monatsschr. Kinderh. 102:135, 1954.
43. Fertman, M. B.: Newer concepts of experimental obesity. Arch. Int. Med. 95:794, 1955.
44. Litteral, E. B., and Malamud, N.: Leukemia with predominant neurologic manifestations. Neurology 5: 740, 1955.
45. Gallais, P., and Collomb, H.: Leucoses à début neurologique; à propos de deux observations. Presse méd. 63:1090, 1955.
46. Andreani, F., Sala, E., and Vercillo, L.: Su di un caso di leucemia acuta iniziato con paralisi periferica del facciale. Minerva med. 47:1816, 1956.
47. Mondzain, M., Garre, H., and Descuns, P.: Leucose aiguë à début neurologique. Algérie méd. 60:1047, 1956.
48. Joseph, M. C., and Levin, S. E.: Leukaemia and diabetes insipidus; case report, with an unexpected effect of cortisone. Brit. M. J. 1:1328, 1956.
49. Kovacs, K., and Monus, Z. B.: Diabetes insipidus syndrome developed with myelocytic leukaemia. Schweiz. Ztschr. allg. Path. 19:278, 1956.
50. Dost, F. H.: Leukämische Meningopathie und Iridopathie beim Kind. Ärzt. Wochen. 11:1070, 1956.
51. Yohe, R. M.: Neurologic symptoms as initial manifestation of acute leukemia. J. Iowa M. Soc. 47:249, 1957.
52. Gibert, E. F., and Rice, E. C.: Neurological manifestations of leukemia. Report of 3 cases in children simulating acute bacterial meningitis. Pediatrics 19: 801, 1957.
53. Sullivan, M. P.: Intracranial complications of leukemia in children. Pediatrics 20:757, 1957.
54. Gordon, D. S.: The nervous system in the reticuloses. Brit. J. Clin. Pract. 11:119, 1957.
55. Yunis, A. A., and Harrington, W. J.: Clinical use of methyl prednisolone in certain hematologic disorders. Metabolism 7:543, 1958.
56. Allies, F.: Adipositas und Polyphagie bei Leukämie. Monatsschr. Kinderh. 106:237, 1958.
57. Farber, S.: Clinical pathological conference. J. Pediat. 53:349, 1958.
58. Whiteside, J. A., Philips, F. S., Dargeon, H. W., and Burchenal, J. H.: Intrathecal amethopterin in neurologic manifestations of leukemia. Arch. Int. Med. 101:279, 1958.
59. Hyman, C. B., Brubaker, C. A., and Sturgeon, P.: Intrathecal methotrexate in the treatment of CNS complications of acute leukemia. Clin. Res. Proc. 7:93, 1959.
60. Hyman, C. B., Brubaker, C. A., Borda, E. C., Hammond, D., and Sturgeon, P.: Treatment of central nervous system leukemia in children. Proc. Am. Assn. Cancer Res. 3:29, 1957.
61. Holland, J. F.: Personal communication.
62. Burchenal, J. H., Ellison, R. R., Murphy, M. L., Karnofsky, D. A., Sykes, M. P., Tan, T. C., Mermann, A. C., Yuceoglu, M., Myers, W. P. L., Krakoff, I., and Alberstedt, N.: Clinical studies on 6-mercaptopurine. Ann. New York Acad. Sc. 60:359, 1954.
63. Farber, S., Toch, R., Sears, E. M., and Pinkel, D.: Advances in chemotherapy of cancer in man. Advances Cancer Res. 4:1, 1956.
64. Elion, G. B., Bieber, S., and Hitchings, G. H.: The fate of 6-mercaptopurine in mice. Ann. New York Acad. Sc. 60:297, 1954.
65. Freeman, M. V.: The fluorometric measurement of the absorption, distribution, and excretion of single doses of 4-amino-10 methyl-pteroyl-glutamic acid (amethopterin) in man. J. Pharmacol. & Exper. Therap. 122:154, 1958.

66. Clausen, R. E., Jr., Lincoln, A. F., and Silberman, H. K.: Diffuse lymphosarcomatosis of central nervous system simulating infectious polyneuritis. Am. J. Med. 20:292, 1956.
67. Williams, H. M., Diamond, H. D., and Craver, L. F.: The pathogenesis and management of neurological complications in patients with malignant lymphomas and leukemia. Cancer 11:76, 1958.
68. Davison, C., and Michaels, J. J.: Lymphosarcoma with involvement of the central nervous system. Arch. Int. Med. 45:908, 1930.
69. Abbott, K. H., and Adson, A. W.: Primary intracranial lymphosarcoma. Arch. Surg. 47:147, 1943.
70. Radzinski, J. M., and Uznaski, M. E.: Generalized lymphosarcomatosis with marked involvement of the brain. Illinois M. J. 85:87, 1944.
71. Young, G. A., Young, R. H., and Gysin, W. M.: Malignant lymphoma with meningeal and polyradicular infiltration. Nebraska M. J. 30:434, 1945.
72. Kohut, H.: Unusual involvement of the nervous system in generalized lymphoblastoma. J. Nerv. & Ment. Dis. 103:9, 1946.
73. Sparling, H. J., Jr., Adams, R. D., and Parker, F., Jr.: Involvement of the nervous system by malignant lymphoma. Medicine 26:285, 1947.
74. Berg, L.: Hypoglycorrhachia of non-infectious origin: diffuse meningeal neoplasia. Neurology 3:811, 1953.
75. Whisnant, J. P., Siekert, R. G., and Sayre, G. P.: Neurological manifestations of the lymphomas. M. Clin. North America 40:1151, 1956.
76. Goldring, S., and Harford, C. G.: Effect of leucocytes and bacteria on glucose content of the cerebrospinal fluid in meningitis. Proc. Soc. Exper. Biol. & Med. 75:669, 1950.
77. Schwartz, C. W., and Collins, L. C.: The Skull and Brain Roentgenologically Considered. Springfield, Ill., Charles C Thomas, 1951.
78. Hitzig, W. H., and Siebenmann, R. E.: Scheinbare Schädelnahtsprengung bei Leukämie. Helvet. paediat. acta 10:590, 1955.
79. Shane, S. J., and Riley, C.: Tuberculous meningitis; combined therapy with cortisone and antimicrobial agents. New England J. Med. 249:829, 1953.
80. Oppenheimer, J. H., and Riester, W. H.: Influence of cortisone on leptomeningeal reaction induced by talc. Proc. Soc. Exper. Biol. & Med. 83:844, 1953.
81. Kamen, G. F., and Erdman, G. L.: Subdural administration of hydrocortisone in multiple sclerosis: effect of ACTH. J. Am. Geriatrics Soc. 1:784, 1953.

Cervical disk protrusions with compression of the spinal cord

Report of a case

Olle Höök, M.D., Hans Lidvall, M.D., and
Karl-Erik Åström, M.D.

DURING THE last decade, it has been realized that many cases of spastic paraplegia in the elderly are caused by cervical spondylosis with protrusion of the intervertebral disks.[1–3] Only a few reports[4–7] have dealt with postmortem examinations of the vertebral column and spinal cord, however.

The present case seems to merit description, since the patient was under observation for a number of years and was subjected to elaborate neurologic examinations including myelography and studies of the pressure of the cerebrospinal fluid with a special technic.[8] The postmortem examination included angiography of the vertebral arteries.

CASE REPORT

First admission. (Serafimerlasarettet, Department of Neurology, case record 130/1954) A 62-year-old male teacher entered the hospital because of general fatigue and impaired strength in the right leg for nine months and a sense of cold, numbness, and stiffness in both hands for four months before admission. He had found it difficult to handle small objects and needed an increasingly longer time in the morning to dress and go to his work. He had been mentally depressed for several years but was otherwise well until the onset of his disability.

Physical examination showed the patient to be well nourished and in no acute distress. Neurologic examination showed him to be somewhat depressed but alert, cooperative, and well oriented. Slight weakness was noted in both hands and the right leg. Sensibility to light touch, pinprick, and temperature was impaired in both hands, and sensibility to position and vibration was slightly impaired in fingers and toes. Muscle reflexes were increased in the legs. The plantar reflex was extensor, and finger flexor jerks and ankle clonus were noted bilaterally. It was difficult for the patient to perform fine finger movements such as buttoning his coat.

Histamine-fast gastric achlorhydria was found but no anemia. The mean corpuscular volume was normal, as were the results of a sternal marrow examination. The blood vitamin B_{12} content was normal. Roentgenograms of the cervical spinal column revealed that disks C5-6 and C6-7 were considerably reduced in height and that large bony ridges on the edges of the corresponding vertebral bodies reduced the width of some of the vertebral foramina considerably (Figs. 1 and 2). Myelography after injections of 0_2 into the subarachnoid space through cisternal puncture demonstrated large protrusions from disks C5-6 and C6-7, which reached the ventral surface of the spinal cord, and smaller protrusions from disks C3-4, C4-5, L3-4, and L4-5. The diameter of the vertebral canal was reduced; the anteroposterior diameter measured 15 mm. at C4. The cerebrospinal fluid pressure was measured and recorded simultaneously at cisternal and lumbar levels before and after compression of the jugular veins, the head being slightly flexed. No block could be demonstrated, and the composition of the cerebrospinal fluid was normal at both levels (Fig. 3).

The diagnosis was cervical myelopathy due to protrusion of intervertebral disks. No operation was deemed necessary at that time.

From the Department of Neurology, Serafimerlasarettet, and the Department of Pathology, Sabbatsbergs sjukhus, Stockholm.

Second admission. (Serafimerlasarettet Department of Neurology, case record 385/1958) During the intervening four and a quarter years, the symptoms had gradually worsened without any remissions. The patient was bedridden during the last months, partly because of his mental depression. He had become constipated, but micturition was normal. He had had no pains in his arms and legs. Neurologic examination showed that the spastic paraplegia had increased; he was now unable to walk without support on both sides. The strength in the arms and hands was much better preserved. The small muscles in both hands were slightly wasted. Sensibility to touch, pain, heat, and cold was somewhat impaired in the hands and feet, as was sensibility to position and vibration in the fingers and toes. After lumbar puncture, the cerebrospinal fluid pressure was measured and recorded with an electromanometer and mingograph (Elema, Sweden). Compression of the jugular veins with the help of a sphygmomanometer cuff around the neck showed that a complete block ensued when the neck was slightly extended (Fig. 4).

The patient died suddenly two weeks after he had entered the hospital.

PATHOLOGIC EXAMINATION

The general autopsy revealed that the immediate cause of death was pulmonary emboli and a fresh myocardial infarction.

Angiographic study of the vertebral arteries was performed after ligation of the cranial part of the basilar artery (Fig. 5). The vertebral artery had been curved and displaced laterally at disks C5-6 and C6-7 on the right and at C5-6 on the left. The lumen was reduced dorsoventrally to about half at 2 places.

A part of the posterior fossa and cervical and upper thoracic spine with the enclosed spinal cord and roots were removed in toto[7] and kept in formalin. The remainder of the spinal cord was taken out separately.

Gross examination. Dissection of the specimen revealed pronounced cervical spondylosis. Vertebrae C5 and C6 were compressed and low, and vertebrae C1 through C4 were displaced posteriorly in relation to the remainder of the cervical spine, which therefore assumed the shape of a bayonet. A vertical line through the ventral aspects of disks C5-6 and C6-7 was

Fig. 1. Radiograph of cervical spine, lateral view, 1954. Narrowing of intervertebral disk spaces C5-6 and C6-7. Osteophytes on edges of their vertebral bodies

Fig. 2. Radiograph of cervical spine, oblique view, 1954, shows narrowing of intervertebral foramina

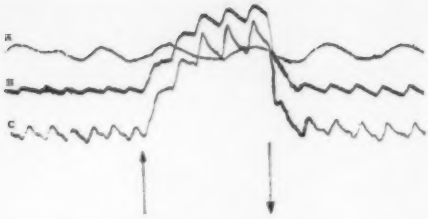


Fig. 3 Cerebrospinal fluid dynamics, first admission, 1954. Mechanical recordings ad modum Antoni and Lagergren. No block demonstrated. [A] Respiration. [B] Pressure of cerebrospinal fluid in cisterna magna. [C] Pressure of cerebrospinal fluid in lumbar region. Patient's head bent slightly forward. Arrows indicate in- and exsufflation of air in cuff around the neck.

situated about 8mm. anterior to a corresponding line through the more cranial disks. Protrusions of the disks were seen between most vertebrae, especially C5-6 and C6-7, where prominent fibrotic, and occasionally bony, elevations had been formed on all sides (Fig. 6), producing transverse ridges across the anterior wall of the vertebral canal. The anteroposterior diameter of the canal was diminished there, and the lumen of the intervertebral foramina was reduced to about one-fifth. Small protrusions were found elsewhere in the cervical spine, but the intervertebral foramina and spinal canal were not reduced in size. A rounded nodular protrusion was seen on the right dorsolateral aspect of disk T1-2, which reduced the diameter of the canal and had the appearance of a local posterior nuclear displacement. The vertebral arteries were in contact with the laterally protruding disks in several places, especially at C5-6 and C6-7, where the vessel had been displaced laterally and partly obstructed. Large apophyseal osteophytes were seen, particularly on the right side of C2 through C5.

The root pouches, ganglia, and dural sheaths of the roots were covered by a layer of connective tissue, which adhered to the walls of the intervertebral foramina and ventrally to the adventitia of the vertebral artery. The duroradicular junctions were usually not smoothly curved but sharpened, because of fibrosis around the root pouch.[9] The radicular nerves of C5 through C8 were outwardly or upwardly directed, the root filaments being angulated at the root ostia.

The spinal cord was flattened and showed indentations corresponding to the dorsally protruding disks. It was considerably reduced in bulk at segment C7, which was in apposition to the large transverse dorsal protrusion of the intervertebral disk of C5-6 (Fig. 7). Division of the cord into segments showed that the lower part of segment C6 and the cranial part of C7 were compressed anteroposteriorly and deformed, especially on the right side. The middle part of C7 was larger but very soft.

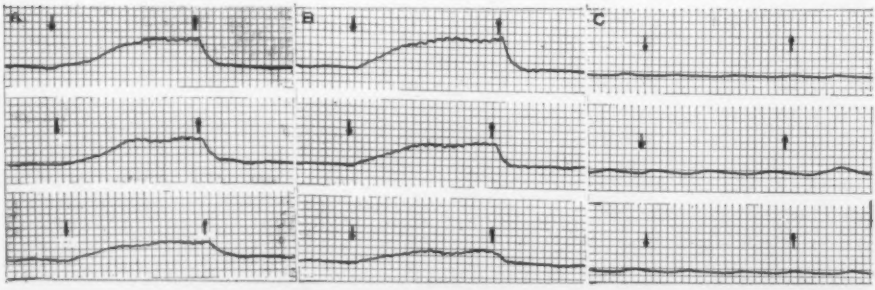


Fig. 4. Cerebrospinal fluid dynamics, second admission, 1958. Recordings of cerebrospinal fluid pressure in lumbar region with electromanometer and mingograph. Arrows indicate in- and exsufflation of sphygmomanometer cuff around the neck. Duration of compression, ten seconds. There was complete block when the head was extended [C] but communication when it was in normal position [A] or flexed [B]. The three curves for the different positions of the head indicate different pressure in the cuff: 60, 75, and 140 mm. Hg respectively.

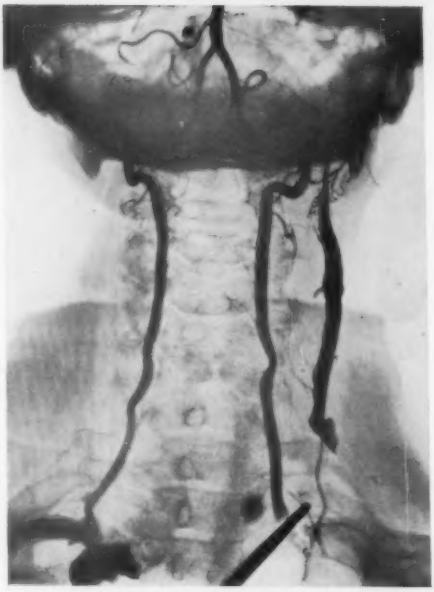


Fig. 5. Postmortem vertebral angiogram. The arteries are displaced laterally at C5-6 and C6-7 on the right and at C5-6 on the left.

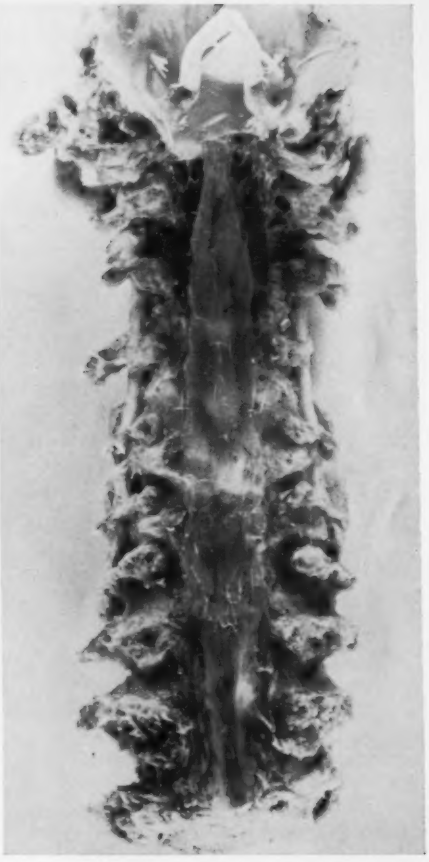


Fig. 6. Anterior surface of cervical canal after laminectomy and removal of spinal cord. Vertebral arteries filled with radiopaque material. Dorsal protrusion of disk C5-6 forms a transverse bar. Smaller dorsolateral protrusion on the right side of C7-T1

Small rounded cavities were found in the dorsal horns of the lower C7 and upper C8 segments, which corresponded to disk C6-7.

Microscopic examination. Pieces of different segments of the spinal cord, roots, ganglia, root pouches of the dura, and the brain stem were embedded in paraffin and celloidin or frozen and stained according to standard neuropathologic methods.

Severe destruction was found in the lower C6 and upper C7 segments, especially on the right side, where the lateral funiculus, root entry zone, and major part of the gray matter had been softened and severely deformed (Fig. 8C). Softening was also noted in the left root entry zone, posterior horn, and lateroventral part of the left anterior horn. Except for a few motoneurons in the ventromedian group and occasional ischemic cells in the intermediate groups, no neurons were seen in the gray matter on either side. Very few transversing myelinated fibers were seen in the gray matter on the right side, although they were rather well preserved on the left side, as was the white commissure bilaterally. Severe loss of myelinated fibers was seen in the right lateral funiculus and in the deep and lateral parts of both posterior funiculi. Many fibers had been destroyed in the left lateral funiculus also, while the anterior funiculi were relatively best preserved. The softened regions contained large numbers of macrophages, whereas there

Fig. 7. Anterior surface of cervical cord with meninges and roots. Transverse indentation caused by protrusion of disk C5-6. Root sleeve fibrosis

was rather cell-poor astrogliotic scar tissue in the solid regions of destruction. The arachnoid membrane was thickened and adhered to the pia on the dorsolateral aspect on the right side. A few round cells and pigment-filled macrophages were noted in the subarachnoid space. The walls of the blood vessels were thickened everywhere, mainly because of an increase of the adventitia, but all were patent. The veins were numerous, dilated, and prominent within the areas of destruction.

The lower part of the C7 and the upper part of the C8 segment showed only moderate compression of the right half but were nevertheless severely affected (Fig. 8D). The intermediate regions of the gray matter had been replaced by cell-poor, loose, astrogliotic tissue that contained rare ischemic neurons. The posterior part of the segment contained 2 symmetrically situated cavities that occupied the posterior horns and the adjacent regions of the posterior and lateral columns. The ventral and medial parts of the anterior horns were comparatively well preserved and contained a number of unimpaired motoneurons. There was a heavy loss of mylinated fibers in the posterior and lateral funiculi, and the propriospinal fibers close to the ventral horns had also degenerated. Many macrophages and astrocytes were found within the affected regions in the posterior horns and posterior funiculi in contrast to the cell-poor tissue in the intermediate regions of the gray matter. Extensive descending degeneration was seen in the lateral funiculi of the T1 and T2 segments, especially on the right side, and some fibers had also disappeared in the interfascicular and septomarginal fasciculi of the posterior funiculi. Descending degeneration in a decreasing degree could be followed in the lateral funiculi down to the lowest lumbar segments (Fig. 8E and F). The gray matter was unaffected everywhere except in the lower cervical cord as described above.

Ascending degeneration and compensatory astrocytosis were noted in the posterior and lateral funiculi from the C5 segment upward (Fig. 8A and B). The zone of degenerated fibers in the posterior funiculi shifted medially due to the consecutive addition of normal elements from the upper cervical roots.

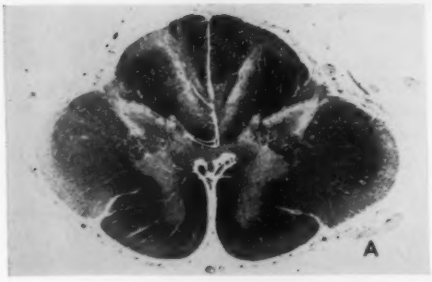
Most fibers in the C7 roots had been destroyed and were replaced by fibrous tissue. Many nerve cells had disappeared in the corresponding ganglia. The fibers were much better preserved in the C6, C8, and T1 roots, even though a number of nerve cells in their ganglia were lacking.

No signs of disease were found elsewhere in the central nervous system.

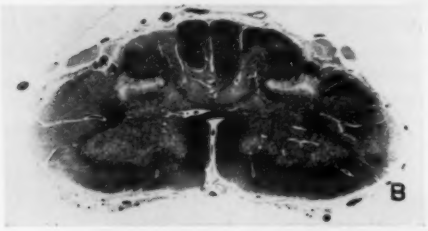
DISCUSSION

The clinical diagnosis of cervical myelopathy due to intervertebral disk protrusions was based upon the history, signs, symptoms, and roentgenograms, including myelograms. Sub-

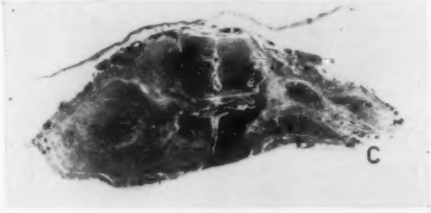
Fig. 8. Transverse Sections of Spinal Cord at Different Levels
(Loyez myelin stain × 16)



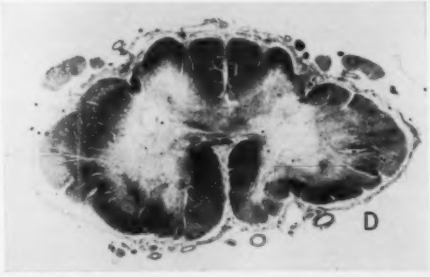
C3, upper part, showing ascending degenerations in posterior and lateral columns



C6, upper part, showing ascending degenerations in dorsal and lateral funiculi

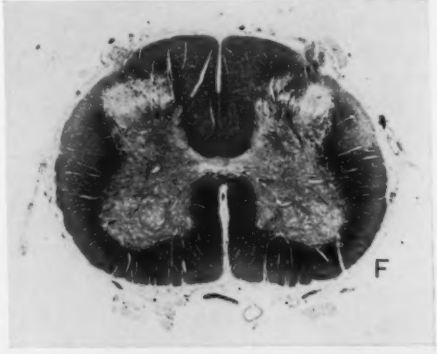


C7, upper part, showing severe destruction and compression of the spinal cord at the level of the protruding disk C5-6



C7, lower part, showing severe degeneration of gray matter and adjacent parts of white matter. Cavity is seen in one dorsal horn. Sections from C8 showed cavities in both dorsal horns.

T2, showing moderate descending degeneration in lateral funiculi



L5, showing slight descending degeneration in dorsal part of lateral funiculi

acute combined degeneration had been excluded by the normal blood and sternal marrow tests and a normal blood B_{12} content. The diagnosis was confirmed by the postmortem examination, which showed that the basic disorder was severe cervical spondylosis.

The signs, symptoms, and history of a progressing disability is in accordance with other reports on this condition.[1,6,10] The patient had no pains in the arms or other clear-cut signs of cervical root compression,[9] which is in agreement with the lack of degeneration in the root fibers. This is remarkable in view of the diminution of several of the intervertebral foramina and the fibrosis of the corresponding root sleeves, but other observers[1] have made similar observations in cases of severe cervical spondylosis.

The damaged region comprised the main part of the gray substance, root entry zones, and large parts of the lateral and posterior funiculi. The shape of the lesion was similar to that in other reported cases,[1,4–7] which indicates the action of some consonant pathogenic factors. It must have been of major importance, of course, that the limited necrosis in the lower C6 through 8 segments was in apposition to the dorsally protruding disks of C5-6 and C6-7. The exact mechanism is still a matter for conjecture, although the histologic appearance of the lesion in transverse sections clearly indicates the role of vascular factors.[5] We do not believe, however, that obstruction of branches from the anterior spinal artery alone can account for the whole destruction, as stated by Mair and Druckman,[6] for the following reasons:

The lesion did not extend longitudinally above or below the protruded disks, as should have occurred, and the damaged area must have received blood from branches of both the anterior and posterior spinal arteries according to the studies of Kadyi,[11] Herren and Alexander,[12] and Suh and Alexander.[13] The detailed and excellent monograph of Kadyi clearly states that the anterior spinal artery supplies mainly the gray matter, that its branches never reach the periphery, that there is a border zone comprising gray and white matter, which receives capillaries from both the peripheral and anterior spinal arteries, and, finally, that the root entry zone and apex of the posterior horn exclusively receive branches from the posterior spinal artery.

The lesion was not uniform but made up of smaller areas of different ages and types of ischemic necrosis; there was no uniform liquefaction necrosis such as that seen after thrombosis of the anterior spinal artery.[14–16] Furthermore, all the blood vessels were patent and did not show any signs of recent or previous thrombosis. We conclude, therefore, that the lesion was due to successive and temporary occlusion of different branches, mainly from the anterior spinal artery but also, in part, from the peripheral arteries. The basic cause of compression of the blood vessels was the dorsal protrusion of the intervertebral disks with concomitant decrease of the anteroposterior diameter of the vertebral canal.[7] Anterior fixation of the spinal cord to the dentate ligament was probably an important subsidiary factor.

The bulging and the partial obstruction of the vertebral arteries were due to the lateral protrusion of disks C5-6 and C6-7.[17,18] It is possible that ischemia of the spinal cord was increased thereby.

The blocking of the subarachnoid space when the head was extended might have been caused by bulging of the ligamentum flavum.[19] It is conceivable that the spinal cord, with its arteries, could be compressed and traumatized between a fold of this ligament and the prominent edges of the dorsally protruding disks. This and other similar cases of cervical disk protrusion (to be reported separately) have convinced us of the necessity of performing Queckenstedt's test with the patient's head in different positions.[20]

SUMMARY

Cervical myelopathy due to spondylosis with disk protrusions in a 62-year-old man is described. The case was followed more than four years, and the examinations included myelograms and recordings of the cerebrospinal fluid pressure with the head in different positions. There was a complete spinal block when the head was extended.

It is concluded that the mechanism of producing damage to the spinal cord was probably due to successive and temporary occlusion of different arterial branches, mainly from the anterior spinal artery but, also, in part, from the peripheral arteries. The basic cause of compression of the blood vessels was probably the dorsal protrusion of the intervertebral disks with concomitant decrease of the anteroposterior diameter of the vertebral canal.

REFERENCES

1. Brain, W. R., Northfield, D., and Wilkinson, M.: The neurological manifestations of cervical spondylosis. Brain 75:187, 1952.
2. Yuhl, E. T., Hanna, D., Rasmussen, T., and Richter, R. B.: Diagnosis and surgical therapy of chronic midline cervical disk protrusions. Neurology 5:494, 1955.
3. Clarke, E., and Robinson, P. K.: Cervical myelopathy: a complication of cervical spondylosis. Brain 79: 483, 1956.
4. Bedford, P. D., Bosanquet, F. D., and Russell, W. R.: Degeneration of the spinal cord associated with cervical spondylosis. Lancet 2:55, 1952.
5. Greenfield, J. G.: Malformations et dégénérescences des disques intervertébraux de la région cervicale. Rev. méd. Suisse Rom. 73:227, 1953.
6. Mair, W. G. P., and Druckman, R.: The pathology of spinal cord lesions and their relation to the clinical features in protrusion of cervical intervertebral discs. Brain 76:70, 1953.
7. Payne, E. E., and Spillane, J. D.: The cervical spine. An anatomico-pathological study of 70 specimens (using a special technique) with particular reference to the problem of cervical spondylosis. Brain 80:571, 1957.
8. Höök, O., and Lidvall, H.: Unpublished observations.
9. Frykholm, R.: Cervical nerve root compression resulting from disc degeneration and root-sleeve fibrosis. Acta chir. scandinav. supp. 160:1, 1951.
10. Pallis, C., Jones, A. M., and Spillane, J. D.: Cervical spondylosis; incidence and implications. Brain 77:274, 1954.
11. Kadyi, H.: Über die Blutgefässe des Menschlichen Rückenmarkes. Lemberg, 1889.
12. Herren, R. Y., and Alexander, L.: Sulcal and intrinsic blood vessels of human spinal cord. Arch. Neurol. & Psychiat. 41:678, 1939.
13. Suh, T. H., and Alexander, L.: Vascular system of the human spinal cord. Arch. Neurol. & Psychiat. 41: 659, 1939.
14. Spiller, W. G.: Thrombosis of the cervical anterior median spinal artery; syphilitic acute anterior poliomyelitis. J. Nerv. & Ment. Dis. 36:601, 1909.
15. Zeitlin, H., and Lichtenstein, B. W.: Occlusion of the anterior spinal artery. Arch. Neurol. & Psychiat. 36:96, 1936.
16. Steegmann, A. T.: Syndrome of the anterior spinal artery. Neurology 2:15, 1952.
17. Kovacs, A.: Kephalalgia e Subluxatione artic. cervicalis. Fortschr. Geb. Röntgenstrahlen 85:142, 1956.
18. Kaplan, L., and Kennedy, F.: The effect of head posture on the manometrics of the cerebrospinal fluid in cervical lesions; a new diagnostic test. Brain 73: 337, 1950.
19. Taylor, A. R.: Mechanism and treatment of spinal-cord disorders associated with cervical spondylosis. Lancet 1:717, 1953.
20. Krogdahl, T., and Torgersen, O.: Die "Unco-vertebralgelenke" und die "Arthrosis deformans unco-vertebralis." Eine pathologisch-anatomische und röntgenologische Studie. Acta radiol. 21:231, 1940.

Adrenocortical function in epilepsy

I. The role of cortisol (hydrocortisone) in the mechanism and management of seizures

Patrick F. Bray, M.D., Robert S. Ely, M.D.,
Gerardo Zapata, M.D., and Vincent C. Kelley, M.D., Ph.D.

CERTAIN CLINICAL and experimental observations indicate that adrenocortical hormones have an influence on various functions of the central nervous system. Mental disturbances, electroencephalographic abnormalities, intracranial hypertension, and convulsions reflect alterations in adrenocortical function and occur with either a lack or an excess of hormones produced by the adrenal cortex. Hartman, Beck, and Thorn[1,2] have called attention to the occurrence of mental disturbances in patients with Addison's disease and pointed out that the administration of adrenocortical extract alleviated these symptoms. In patients with rheumatoid arthritis being treated with cortisone, changes in mood and mentation[3,4] have been produced. These altered mental states can be reversed by discontinuing the medication. When ACTH, cortisone, or hydrocortisone is given therapeutically or experimentally, electroencephalographic abnormalities can occur.[5-7] Hypoadrenocorticism, as it occurs in patients with Addison's disease, has been associated with electroencephalograms that have abnormally slow frequencies. Several groups have reported such findings,[8-10] and one group[10] demonstrated that adrenocortical extract restored normal brain wave patterns, whereas DCA failed to produce this effect.

Increased intracranial pressure complicating steroid therapy has been noted by a number of observers,[11] including the authors. The pathogenesis of this pressure is not clear, but it seems to be directly related to hormone therapy rather than to the underlying disease because the intracranial hypertension clears upon withdrawal of steroids.

Convulsions, even status epilepticus, may occur in patients receiving cortisone[12,13] and ACTH.[14] ACTH has been shown to have little effect on the seizure threshold in rats,[15] whereas cortisone and cortisol cause significant lowering of electroshock threshold[16] (an increased susceptibility to seizures). Conversely, DCA produced an appreciable elevation of electroshock threshold[17] (a diminished susceptibility to seizures). McQuarrie, Anderson, and Ziegler[18] reported that DCA was therapeutically useful in two patients with epilepsy, and similar results were reported by Aird and Gordon.[19] The treatment of seizures with ACTH and cortisone has been attempted,[20-22] but these drugs have never become established anticonvulsants.

Since Dilantin is generally conceded to be one of the most effective anticonvulsants in use, its mode of action has been widely studied. Some have wondered whether its effect has been linked with the pituitary-adrenal system. Woodbury[23] found that Dilantin causes hypertrophy of the adrenal gland in rats, suggesting a hyperfunctioning gland. At that time, changes in adrenal gland weight in animals was considered a good method for assaying the effect of a drug on the pituitary-adrenal system.[24] This stimulated Bray, Ely, and Kelley[25] to study the blood adrenal hormone concentrations in a small group of epileptic children. In these patients, the plasma 17-hydroxycorticosteroid levels were normal, but it was found that the Dilantin-treated epileptic children re-

From the Department of Pediatrics, University of Utah College of Medicine, Salt Lake City, and the Utah State Training School, American Fork, Utah.

This work was supported in part by Research Grant B1240 from the National Institute for Neurological Diseases and Blindness. The authors are also indebted to Parke-Davis and Co. for helping to defray the publication costs.

Dr. Zapata's present address is the School of Public Health, Harvard University, Boston. Dr. Kelley is now with the Department of Pediatrics, University of Washington School of Medicine, Seattle.

sponded less well to an ACTH stimulus than did those in the other groups studied. Christy and Hofmann[26] confirmed this finding in the children they studied but noted normal ACTH responsiveness in adults. Several groups of workers[27–30] have studied urinary excretion of 17-ketosteroids and corticoids in epileptic patients and other patients receiving electroshock therapy. Although considerable individual variation has been noted, in general, the excretion of 17-ketosteroids and reducing corticoids has been lower than normal. In one of these studies,[30] this decreased output of 17-ketosteroids and corticoids was attributed to Dilantin rather than to the influence of epilepsy.

From these various clinical observations, one can say that biologically active adrenal hormones are important in maintaining homeostasis of the central nervous system, although the mode of their action is obscure. In an effort to determine whether the functional state of the pituitary-adrenal system is an important clinical factor in either the mechanism or the management of epilepsy, a comprehensive investigation of adrenocortical function and the metabolism of adrenal steroids in patients with this disorder has been undertaken. In this investigation, laboratory methods that directly measure the concentration of adrenal hormones in the blood and urine have been employed.

Basic outline of adrenal steroid function. The adrenal steroids have two basic actions, either a glucocorticoid or a mineralocorticoid effect. Hydrocortisone (hereafter referred to as cortisol for the sake of chemical correctness) and cortisone primarily affect the metabolism of certain organic compounds, the so-called glucocorticoid effect. Aldosterone and DCA strongly influence the metabolism of certain inorganic compounds, the so-called mineralocorticoid effect. Cortisol, aldosterone, and corticosterone are the principal hormones produced by the human adrenal cortex. Cortisone and DCA, although functionally important, are synthetic products.

Outline of study program. At the time this study was begun, technics were available for quantitating cortisol and corticosterone in plasma. Furthermore, since these are the two adrenal hormones present in the highest concentration in human blood, attention was focused on them.

The present report is concerned with the initial phase of this study, an attempt to evaluate the production and "metabolism" of cortisol in treated and untreated epileptic patients. The technics employed are not specific for cortisol but measure all 17-hydroxycorticosteroids (17-OHCS). These studies include determination of [1] plasma levels of 17-OHCS, [2] the response of plasma levels of 17-OHCS to an ACTH stimulus, [3] the in vivo half life of cortisol (measured as 17-OHCS), and [4] urinary excretion of 17-OHCS.

The data on the "metabolism" of corticosterone will be published in a later paper.

MATERIALS AND METHODS

The study group of epileptic patients was divided into 3 categories: 29 Dilantin-treated patients, 6 phenobarbital-treated patients, and 12 untreated patients. All of these patients were residents of the Utah State Training School, and all were mentally retarded. Of the 47 patients, 10 had spastic cerebral palsy; the incidence of spasticity was similar in each group. All of the patients had grand mal seizures, and some had focal motor or psychomotor episodes; none had petit mal epilepsy. The patients were not classified neurologically in any greater detail. Patients ranged in age from 4 to 49 years, but the majority were in the second, third, and fourth decades of life. The 3 groups studied included 32 females and 15 males, and the sex ratio was similar in each of the groups.

Plasma samples were separated by centrifugation and stored in a freezer until used for analysis. Plasma 17-OHCS concentrations were determined by the method of Nelson and Samuels[31] as modified by Eik-Nes, Nelson, and Samuels.[32] The response of plasma 17-OHCS concentration to ACTH also was studied in most patients. A single intravenous injection of ACTH, 0.2 international units per kilogram, was given after a control blood specimen had been obtained. One hour later, another blood sample was obtained and the difference between the plasma 17-OHCS concentrations in these 2 samples was taken as the "17-OHCS response to ACTH."

For determination of the half life of cortisol, the steroid (free alcohol), commercially prepared in a 0.5% solution in 50% ethanol

TABLE 1
COMPARISON OF EPILEPTIC AND NORMAL SUBJECTS

Group	Number	Plasma 17-OHCS concentration (μg. %) Mean	SEM	P	Number	17-OHCS response to ACTH* (μg. %) Mean	SEM	P
Controls	160	11.0	0.5	—	25	14.4	1.9	—
Untreated epileptics	9	15.0	4.4	>0.1	5	17	4.9	>0.1
Dilantin-treated epileptics	33	15.4	3.8	>0.1	14	14.2	3.3	>0.1
Phenobarbital-treated epileptics	6	15.0	9.2	>0.1	5	23	9.8	>0.1

Group	Number	Cortisol half life (minutes) Mean	SEM	P	Number	Urinary 17-OHCS (mg. per 24 hours) Mean	SEM	P
Controls	12	98.3	2.9	—	24	3.6	0.7	—
Untreated epileptics	7	94	9.8	>0.1	7	2.2	0.5	<0.01
Dilantin-treated epileptics	31	91	7.0	>0.1	29	2.0	0.9	<0.01
Phenobarbital-treated epileptics	6	119	26.0	>0.1	7	2.6	0.6	<0.01

*Increase in plasma 17-OHCS concentration one hour after intravenous injection of 0.2 international units of ACTH per kilogram

(Cortef I.V. furnished through the courtesy of Dr. D. J. O'Donovan, The Upjohn Company, Kalamazoo, Mich.), was mixed with 150 cc. of 5% dextrose solution and given intravenously in approximately thirty minutes. The dose of cortisol was 1 mg. per kilogram of body weight. Blood samples for 17-OHCS determinations were obtained at zero, thirty, sixty, ninety, one hundred twenty, and one hundred eighty minutes. In each case, the logarithms of the 17-OHCS concentrations were plotted against time and the cortisol half-life value, expressed in minutes, was calculated from the slope of the regression line.[33]

Urinary 17-OHCS were determined from twenty-four-hour urine collections by the method of Glenn and Nelson.[34]

RESULTS

Table 1 shows the mean plasma levels of 17-OHCS in each of the study groups. None of these mean concentrations differs significantly from normal. It is also apparent from the standard error of the mean for each study group that considerable variation exists.

Table 1 indicates the plasma 17-OHCS response in these patients to a standard ACTH stimulus. The mean increases in the epileptic

TABLE 2
COMPARISON OF WELL-CONTROLLED AND POORLY CONTROLLED DILANTIN-TREATED EPILEPTICS

Group	Number	Plasma 17-OHCS concentration (μg. %) Mean	SEM	P	Number	17-OHCS response to ACTH* (μg. %) Mean	SEM	P
Well-controlled	25	11.0	1.1	—	18	15.2	1.7	—
Poorly controlled	7	40.9	13.6	>0.02 <0.05	6	14.0	3.5	>0.1

Group	Number	Cortisol half life (minutes) Mean	SEM	P	Number	Urinary 17-OHCS values (mg. per 24 hours) Mean	SEM	P
Well-controlled	24	94.0	8.8	—	22	1.8	0.5	—
Poorly controlled	7	80.0	12.4	>0.1	6	0.8	0.34	>0.1

*Increase in plasma 17-OHCS concentration one hour after intravenous injection of 0.2 international units of ACTH per kilogram

groups studied do not differ significantly from that in the normal group.

Table 1 shows the half-life values, which reflect the rate at which intravenously administered cortisol disappears from the circulation. In none of the study groups is the half life significantly different from that in the normal group.

The data in Table 1 indicate that all of the epileptic groups studied have significant reductions in their twenty-four-hour urinary excretions of 17-OHCS.

The groups of Dilantin-treated patients have been subdivided into well-controlled and poorly controlled patients, and the data concerning them are compared in Table 2. The control levels of 17-OHCS appear to be somewhat higher in the poorly controlled patients, but the 17-OHCS responses to ACTH are not different in the 2 groups nor are the half-life values and twenty-four-hour urinary 17-OHCS excretions.

DISCUSSION

The results of this study indicate that patients with epilepsy, as a group, either treated or untreated, have normal plasma levels of 17-OHCS, normal response of 17-OHCS to an ACTH stimulus, and normal cortisol half-life values. However, the twenty-four-hour urinary excretion of 17-OHCS is significantly reduced in all of the epileptic groups studied. This, considered with the observation of Costa and Bonnycastle[20] of decreased 17-ketosteroid urinary excretion, suggests that the total functional capacity of the adrenal cortex is reduced. However, the decreased excretion of 17-OHCS and 17-ketosteroids might reflect alterations in the metabolism of adrenal steroids rather than in their production. If such were the case, these substances might be excreted in the urine in some form other than either 17-OHCS or 17-ketosteroids.

Among the Dilantin-treated epileptic patients, the small group designated as poorly controlled had elevated plasma 17-OHCS concentrations. However, this group failed to differ from the well-controlled patients in terms of their 17-OHCS response to ACTH, cortisol half-life values, or twenty-four-hour urinary output of 17-OHCS. Furthermore, the majority of the Dilantin-treated patients had normal plasma concentrations of these steroids; this is compatible with Woodbury's[23] demonstration that, in rats, administration of Dilantin does not produce elevated blood cortisol concentrations. No obvious explanation is apparent for the elevated 17-OHCS concentrations observed in the poorly controlled Dilantin-treated patients.

The ACTH–17-OHCS response test employed in the present study (the one-hour response to 0.2 international units of ACTH per kilogram, intravenously) revealed no significant difference between the response in any group of epileptic patients and that in the normal control group. This latter finding fails to confirm the observation of decreased ACTH responsiveness in Dilantin-treated epileptic patients previously reported.[25] However, this may be attributable to differences in technic, since, in the previous study, the two-hour response of plasma 17-OHCS concentration to the intramuscular injection of 25 international units of ACTH was employed.

SUMMARY

In an attempt to evaluate the role of cortisol in epilepsy, measurements were made of plasma levels of 17-OHCS, plasma 17-OHCS responses to an ACTH stimulus, cortisol half life, and urinary 17-OHCS excretion in epileptic patients. The groups included in this study were [1] untreated epileptic patients, [2] patients on long-term Dilantin therapy, [3] patients on long-term phenobarbital therapy, and [4] control subjects.

The epileptic study groups differed from the control subjects in only one respect: all of these patients had significantly reduced amounts of 17-OHCS in their urine. However, when the group of Dilantin-treated epileptic patients was arbitrarily subdivided, certain differences became apparent. A small group of poorly controlled patients had plasma 17-OHCS levels that were somewhat higher than those in the larger, well-controlled group. The clinical significance of the latter observation is not apparent.

In summary, it seems unlikely from these studies that hydrocortisone plays an important role in the mechanism or treatment of seizures.

The authors wish to express their appreciation to Doris F. Tippit and Richard B. Young for their technical assistance.

REFERENCES

1. Hartman, F. A., Beck, G. M., and Thorn, G. W.: Improvement in nervous and mental states under cortin therapy. J. Nerv. & Ment. Dis. 77:1, 1933.
2. Hartman, F. A.: The adrenal problem. Endocrinology 19:633, 1935.
3. Lidz, T., Carter, J. D., Lewis, B. I., and Surratt, C.: Effects of ACTH and cortisone on mood and mentation. Psychosom. Med. 14:363, 1952.
4. Clark, L. D., Quarton, G. C., Cobb, S., and Bauer, W.: Further observations on mental disturbances associated with cortisone and ACTH therapy. New England J. Med. 249:1, 1953.
5. Pine, I., Engel, F. L., and Schwartz, T. B.: The electroencephalogram in ACTH and cortisone treated patients. Electroencephalog. & Clin. Neurophysiol. 3: 301, 1951.
6. Friedlander, W. J., and Rottger, E.: The effect of cortisone on the electroencephalogram. Electroencephalog. & Clin. Neurophysiol. 3:311, 1951.
7. Glaser, G. H., Kornfeld, D. S., and Knight, R. P.: Intravenous hydrocortisone, corticotropin and the electroencephalogram. Arch. Neurol. & Psychiat. 73:338, 1955.
8. Condon, J. V., Becka, D. R., and Gibbs, F. A.: Electroencephalographic abnormalities in endocrine disease. New England J. Med. 251:638, 1954.
9. Engel, G. L., and Margolin, S. G.: Neuropsychiatric disturbances in Addison's disease and role of impaired carbohydrate metabolism in production of abnormal cerebral function. Arch. Neurol. & Psychiat. 45:881, 1941.
10. Engel, G. L., and Margolin, S. G. Neuropsychiatric disturbances in internal disease. Arch. Int. Med. 70: 236, 1942.
11. Dees, S. C., and McKay, H. W.: Occurrence of pseudotumor cerebri (benign intracranial hypertension) during the treatment of children with asthma by adrenal steroids. Pediatrics 23:1143, 1959.
12. Stephen, E. H. M., and Noad, K. B.: Status epilepticus occurring during cortisone therapy. M. J. Australia 2:334, 1951.
13. Good, R. A., Vernier, R. L., and Smith, R. T.: Serious untoward reactions to therapy with cortisone and adrenocorticotoropin in pediatric practice (Part I). Pediatrics 19:93, 1957.
14. Dorfman, A., Apter, N. S., Smull, K., Bergenstal, D. M., and Richter, R. B.: Status epilepticus coincident with use of pituitary adrenocorticotropic hormone. J.A.M.A. 146:25, 1951.
15. Woodbury, D. M., Cheng, C. P., Sayers, G., and Goodman, L. S.: Antagonism of adrenocorticotrophic hormone and adrenal cortical extract to desoxycorticosterone; electrolytes and electroshock threshold. Am. J. Physiol. 160:217, 1950.
16. Fingl, E., Olsen, L. J., Harding, B. W., Crockett, A. J., and Goodman, L. S.: Effects of chronic anticonvulsant administration upon cortisone-induced brain hyperexcitability. J. Pharmacol. & Exper. Therap. 105:37, 1952.
17. Woodbury, D. M.: Effect of Hormones on Brain Excitability and Electrolytes. Recent Progress in Hormone Research. Proc. of the Laurential Hormone Conference, New York, Academic Press, Inc., 1954.
18. McQuarrie, I., Anderson, J. A., and Ziegler, M. R.: Observations on the antagonistic effects of posterior pituitary and cortico-adrenal hormones in the epileptic subject. J. Clin. Endocrinol. 2:406, 1942.
19. Aird, R. B., and Gordon, G. S.: Anticonvulsive properties of desoxycorticosterone. J.A.M.A. 145:715, 1951.
20. Klein, R., and Livingston, S.: Effect of adrenocorticotropic hormone in epilepsy. J. Pediat. 37:733, 1950.
21. Glaser, G. H., and Merritt, H. H.: Effects of corticotropin (ACTH) and cortisone on disorders of the nervous system. J.A.M.A. 148:898, 1952.
22. Low, N. L.: Infantile spasms with mental retardation II. Treatment with cortisone and adrenocorticotropin. Pediatrics 22:1165, 1958.
23. Woodbury, D. M.: Effects of chronic administration of anticonvulsant drugs, alone and in combination with desoxycorticosterone, on electroshock seizure threshold and tissue electrolytes. J. Pharmacol. & Exper. Therap. 105:46, 1952.
24. Sayers, G.: The adrenal cortex and homeostasis. Physiol. Rev. 30:241, 1950.
25. Bray, P. F., Ely, R. S., and Kelley, V. C.: Studies of 17-hydroxycorticosteroids. VIII. Adrenocortical function in patients with convulsive disorders. Arch. Neurol. & Psychiat. 72:583, 1954.
26. Christy, N. P., and Hofmann, A. D.: Effects of diphenylhydantoin upon adrenal cortical function in man. Neurology 9:245, 1959.
27. Hemphill, R. E., MacLeod, L. D., and Reiss, M.: Changes in the output of 17-ketosteroids after shock treatment, pre-frontal leucotomy and other procedures. J. Ment. Sc. 88:554, 1942.
28. Ashby, W. R.: Effects of convulsive therapy on the excretion of cortins and ketosteroids. J. Ment. Sc. 95: 275, 1949.
29. Costa, P. J., and Bonnycastle, D. D.: Adrenal function in women with chronic epilepsy. J.A.M.A. 149:1093, 1952.
30. Costa, P. J., Glaser, G. H., and Bonnycastle, D. D.: Effects of diphenylhydantoin (Dilantin) on adrenal cortical function. Arch. Neurol. & Psychiat. 74:88, 1955.
31. Nelson, D. H., and Samuels, L. T.: A method for the determination of 17-hydroxycorticosteroids in blood: 17-hydroxycorticosterone in the peripheral circulation. J. Clin. Endocrinol. 12:519, 1952.
32. Eik-Nes, K., Nelson, D. H., and Samuels, L. T.: Determination of 17, 21-hydroxycorticosteroids in plasma. J. Clin. Endocrinol. 13:1280, 1953.
33. Kuipers, F., Ely, R. S., Hughes, E. R., and Kelley, V. C.: Metabolism of steroids II. Half-life of various steroids in dogs. Proc. Soc. Exper. Biol. & Med. 95: 187, 1957.
34. Glenn, E. M., and Nelson, D. H.: A chemical method for the determination of 17-hydroxycorticosteroids and 17-ketosteroids in urine following hydrolysis with β-glucuronidase. J. Clin. Endocrinol. 13: 911, 1953.

Interactions of human sera and spinal fluids with antibrain rabbit sera

Clara H. Williams, Ph.D., and
Frederick W. Barnes, Jr., M.D., Ph.D.

THE AUTHORS found previously[1] that rabbit antiserum to a saline-soluble component of human brain gave a precipitate when mixed with the sera of 14.7% of 115 neuropsychiatric patients tested but gave no reaction when mixed with sera from 128 general medical and surgical patients. Of the positively reacting sera, 13 were from a total of 41 patients with general paresis, representing 31.7%. However, spinal fluids from any human source always gave a precipitate. The precipitin tests were performed by mixing serial dilutions of the antibrain serum with each of the patients' sera diluted 4-fold or undiluted spinal fluids. The dilutions of antisera giving a precipitate ranged from 160- to 2,560-fold for the sera and 8- to 32-fold for the spinal fluid.

The present work contrasts the above with a search for the limits of dilution of each of the human sera in the reaction and thereby gives an indication of the amount of "antigen" in the patients' sera. The limits of both precipitin formation and complement-fixation were sought, the former with 4-fold and the latter with 10-fold dilutions of the rabbit antibrain serum. A group of patients larger than that reported earlier was used in the present work in an attempt to render our previous findings even more conclusive.

MATERIALS AND METHODS

Preparation of antigen. Human brain cortex, 50 gm., was homogenized in 100 cc. of distilled water at 4° C., filtered through gauze, and centrifuged and the supernatant poured off. The sediment was mixed with another 100 cc. of water and centrifuged, and the supernatant was added to the first and stored at −20° C. This water-soluble fraction had a total protein content of 6 mg. per cubic centimeter (Folin-Cicalteau). The sediment remaining after the water fraction had been removed was suspended, then resuspended in a total volume of 200 cc. of saline, and centrifuged and the supernatant collected and stored. The protein content of this fraction was 2.5 mg. per cubic centimeter.

Immunization of rabbits. Each of the 2 brain antigens with the protein content described above (water- and saline-soluble supernatants) were administered twice weekly intraperitoneally to white, male rabbits weighing 5 to 7 lb.; 0.5 cc. was given at each injection for the first three weeks, then 1 cc. for five weeks. If the serum obtained at the trial bleeding eight days after the last injection gave a precipitin or fixed complement with the corresponding brain antigen in sufficiently high dilution, blood was obtained by cardiac puncture on the tenth day. The antiserum reacted with both the water-soluble and saline-soluble antigen fractions in 500-fold dilutions of the antigens; therefore, the fractions were pooled.

Source of human sera and spinal fluids. Sera for precipitin tests were obtained from [1] 180 patients with no mental disorder from the general medical and surgical service, [2] 9 patients with multiple sclerosis, and [3] 264 neuropsychiatric patients, of whom 23 had paresis. Complement-fixation tests were done on 40 of the first group, the 9 patients with multiple sclerosis, and 114 of the neuropsychiatric patients, including 17 of those with paresis. Cerebrospinal fluid was obtained from 40 patients, of whom 6 had paresis, 4 had

From the Psychophysiologic Research Laboratory, Veterans Administration Hospital, Perry Point, Md., and the Departments of Medicine and Physiological Chemistry, Johns Hopkins Medical Institutions and Hospital for Women of Maryland, Baltimore.

TABLE 1
HUMAN SERUM AT VARIOUS DILUTIONS
PRECIPITIN FORMATION WITH ANTIBRAIN RABBIT SERUM*

Type of patient	Number of sera	Number of sera positive	Number of sera giving a precipitin at limiting dilutions shown					
			500	1,000	2,000	4,000	10,000	20,000
Medical and surgical	180	19	4	5	3	2	4	1
Multiple sclerotic	9	1	1 (100-fold)	0	0	0	0	0
Neuropsychiatric (all types)	264	47	15	8	17	5	1	1
Paretic	23	12	1	3	5	3	0	0

*Diluted 5-fold

multiple sclerosis, 23 were from the general medical and surgical wards, and 7 were from neuropsychiatric service.

Precipitin tests were done on a microscale, with adequate controls, by mixing 0.2 cc. of antiserum diluted 4-fold and 0.2 cc. of dilutions of brain antigen, human serum, or spinal fluid ranging from 10- to 500-fold. The tubes were incubated for forty-five minutes at 37° C., stored for eighteen hours at 4° C., centrifuged, and examined for precipitate. Any controls not free of precipitate were discarded.

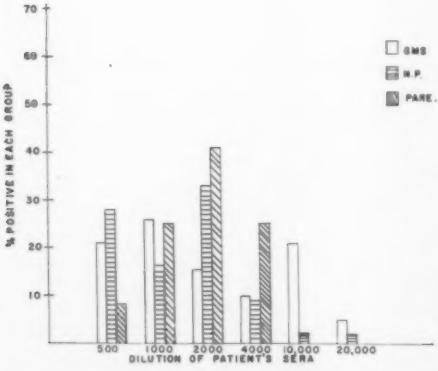


Fig. 1. Comparison of precipitin reactions between antihuman brain rabbit serum and human sera from 3 different patient types. GMS represents general medical and surgical patients, NP represents neuropsychiatric patients, and PARE represents paretic patients. The per cent positive in each group equals 100 times the quotient of the number of sera in that group reacting positively at a given dilution divided by the total number of positives in each group.

Complement-fixation test. A modification of the Kolmer test consisted of mixing 0.2 cc. of a 1:10 dilution of antiserum, 0.2 cc. of dilutions of brain antigen, human serum, or spinal fluid ranging from 100- to 100,000-fold, and 0.1 cc. of guinea-pig complement diluted to contain 2 units; the mixture was then stored overnight at 4° C. Antiserum, human serum, and antigen were inactivated at 52° C. for twenty minutes before use. The next day, 0.2 cc. of a hemolysin dilution containing 2 units and 0.1 cc. of 2% sheep-cell suspension were added; the mixtures were incubated for fifteen minutes at 37° C. and centrifuged. The degree of hemolysis was then estimated by eye. Controls of all reactants were set up for each test, and a test was discarded if any of the reactants were anticomplimentary or naturally hemolytic.

RESULTS

In studying precipitin formation, a screening test was carried out using a 4-fold dilution of antihuman brain rabbit serum and 10-, 100-, and 500-fold dilutions of human sera. If precipitation occurred, it did so at the 500-fold dilution only, not in the lower dilutions. These positively reacting sera were then tested to obtain the limiting dilution of precipitation.

Table 1 shows that these limits ranged from 500- to 10,000-fold. When seen graphically (Fig. 1), the data indicate that, for the majority of sera, the limits of dilution for precipitin formation were between 500- and 4,000-fold; 68% of the 12 positive paretic sera showed a dilution limit of at least 2,000-fold.

TABLE 2
HUMAN SERUM AT VARIOUS DILUTIONS
COMPLEMENT-FIXATION TESTS WITH ANTIBRAIN RABBIT SERUM*

Type of patient	Number of sera	Number of sera fixing complement at limiting dilutions shown						
		500	1,000	5,000	10,000	20,000	50,000	100,000
General medical and surgical	40	10	12	12	3	1	1 (2)+	1 (3)
Multiple sclerosis	9	2	5	2	0	0	0 (1)	0
Neuropsychiatric (all types)	111	26	37	30	10	2	3 (8)	3 (10)
Paretics	17	2	4	8	2	0 (1)	1 (3)	0 (5)

*Diluted 10-fold
+The numbers in parentheses represent those sera which gave a positive complement-fixation reaction below the 5,000-fold dilution (already included in the total) and also at the higher dilution indicated.

From the results, it may be seen that the antibrain serum gave a precipitate with 19 of the 180 sera from the medical and surgical cases (11%), with 1 serum from the 9 multiple sclerosis cases (12%), and with 47 of the 264 sera from the neuropsychiatric cases (18%). The last group contained sera from 23 patients with paresis, of which 12 gave a positive reaction (52%). Precipitin tests with the antibrain serum and brain antigen had a limiting dilution of brain antigen of 500-fold.

The results of complement-fixation reactions between serial dilutions of human serum and a 10-fold dilution of antihuman brain serum are shown in Table 2 and Figure 2. While a large percentage of the sera described in the paragraph above failed to give a positive reaction, all of the sera from each population group reacted positively in the complement-fixation test. This occurred in dilutions of the patients' sera ranging from 500- to 100,000-fold, with the majority showing dilution limits between 500- and 10,000-fold. Evidence that organ antigens are normally present in human sera has been reported before.[2] The complement-fixation test with antibrain serum and human brain antigen was positive in dilutions of the antigen up to 500-fold.

Somewhat unexpected, but still not contradictory, is the fact that, for the paresis patients' sera showing positive precipitin reactions, titers obtained with the complement-fixation test were usually only 1 serial dilution greater than those with the precipitin test. Otherwise, the many instances in which a serum showed a negative precipitin but a positive complement-fixation test were in accord with the generally greater sensitivity of the latter test.

In a few cases (18%), complement was fixed in 500- or 1,000-fold dilutions of the serum, then not fixed until a 50,000- to 100,000-fold dilution was reached, (see the figures in parenthesis in Table 2). This phenomenon, possibly reflecting more than one kind of antigen-antibody system, was present with sera from all types of patients, including 6 of the 12 paresis cases.

The antibrain serum gave a positive precipi-

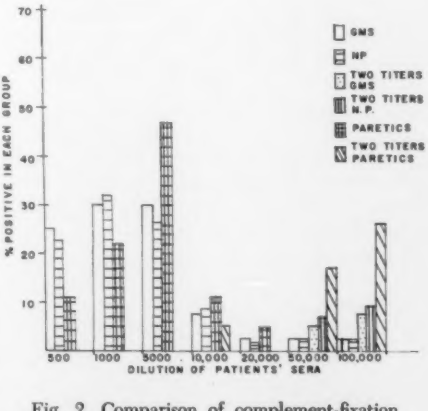


Fig. 2. Comparison of complement-fixation reactions between antihuman brain rabbit serum and human sera from 3 different patient types. See Figure 1. "Two titers" refers to a serum that gave a positive complement-fixation reaction both at dilutions below 5,000-fold and then again at 20-, 50-, or 100,000-fold dilutions.

TABLE 3

HUMAN CEREBROSPINAL FLUID PRECIPITIN FORMATION AND COMPLEMENT-FIXATION WITH ANTIBRAIN RABBIT SERUM*

Type of patient	Number of fluids	Number of cerebrospinal fluids giving a reaction at limiting dilution shown: Precipitin 50	500	1,000	2,000	Number of fluids	100 or below	Complement-fixation 500	1,000	5,000
Medical and surgical	22	18	2	2	0	23	5	11	5	2
Multiple sclerotic	3	3	0	0	0	3	1	2	0	0
Neuropsychiatric	12	5	3	3	1	13	2	6	4	1
Paretic	5	2		2	1	6	1	2	2	1

*Diluted 5-fold for precipitin test and 10-fold for complement-fixation test

tin and a positive complement-fixation test when mixed with serial dilutions of all of the spinal fluids from any source (Table 3). As may be seen, for a few cases, the complement-fixation test was positive even when the spinal fluid was diluted 5,000-fold. The total protein content of the fluids ranged from 12 to 72 mg. per cent; there was no correlation between this value and the degree of dilution possible in the tests.

The fact that the antibrain serum gave higher titers with the human serum than with the homologous brain antigen is interesting.

SUMMARY

The sera of some individuals, in dilutions as high as 20,000-fold, will give a precipitate when mixed with antihuman brain serum. The reaction cannot be immediately related to a particular disease state because sera from 11% of a medical and surgical population reacted positively, as did those from 12% of a group of multiple sclerosis patients and 18% of a neuropsychiatric population. Of the paretic patients' sera, however, 52% did give a precipitate with the antibrain serum. It is apparent that this is not a general flocculation phenomenon.

All of the human sera from any source gave a positive complement-fixation reaction when mixed with antihuman brain rabbit serum. The limiting dilution of some sera was as high as 100,000-fold, but there was no correlation between the limit and the disease state of the patient. Of the total sera tested, 18% fixed complement at dilutions below 500-fold and then again at 50- to 100,000-fold dilutions; this reaction was most evident in the paresis cases (9 out of 17 paretic sera used).

Spinal fluids from all the patients gave a positive precipitin reaction and a positive complement-fixation reaction. No particular clinical correlations are discernable so far, especially between protein content and titer.

These results further suggest the possibility that constituents of the brain circulate in body fluids to a varying degree under varying circumstances.

REFERENCES

1. Williams, C. H., Barnes, F. W., Jr., and Mayer, S. K.: Interactions of human sera and spinal fluids with human brain antigen and antibrain rabbit serum. Proc. Soc. Exper. Biol. & Med. 101:130, 1959.
2. Yeh, S. D., Seip, W. F., Burch, A. B., and Barnes, F. W., Jr.: Tissue specificity of serum components. Arch. Int. Med. 103:933, 1959.

Regeneration of peripheral nerves with hyperinsulin neuronopathy

Report of a case

Edward H. Lambert, M.D., Donald W. Mulder, M.D., and James A. Bastron, M.D.

THE TERM hyperinsulin neuronopathy has been used to describe a syndrome of distal muscular atrophy and paresthesias associated with hyperinsulinism. It has been postulated that the pathophysiology of this syndrome involves both the anterior horn cells and the peripheral nerves, although pathologic evidence for the latter lesion is not available. In a previous review[1] of the history and findings in 20 patients with hyperinsulin neuronopathy associated with pancreatic adenoma, it was found that removal of the pancreatic adenoma resulted in the disappearance of the paresthesias and arrest of progression of the muscular atrophy. Despite this arrest, clear evidence of progressive improvement in muscle strength occurred in only 1 patient, the case reported by Barris.[2] The rarity of significant recovery of muscle has suggested that weakness and atrophy were the result primarily of degeneration of anterior horn cells. In this communication, we wish to describe the occurrence of recovery of muscle strength and muscle bulk after removal of pancreatic adenomas from a patient with hyperinsulin neuronopathy. Electromyographic and other electrodiagnostic tests suggest that recovery in this patient occurred by regeneration of peripheral nerves rather than by sprouting of previously undamaged axons, such as might occur in diseases that affect anterior horn cells.[3] The results of these studies will be described in the following report.

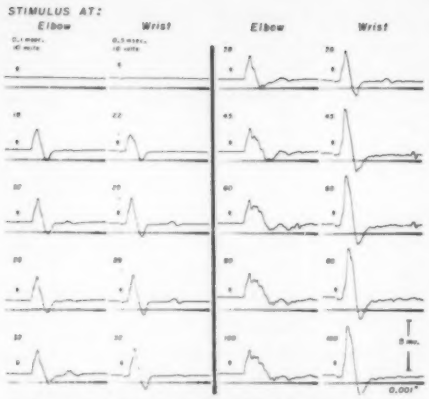
REPORT OF CASE

The patient (Case 11 previously reported by us[1]) was first seen at the Mayo Clinic on February 10, 1955. She had had episodes of confusion for six months and episodes of coma for three months before her examination at the Clinic. Two weeks before admission, she was aware of paresthesia of her hands and feet. Examination revealed weakness of muscles in the distal portions of all 4 extremities. A diagnosis of mutliple endocrine adenomas was established. Operative exploration of the parathyroid gland with removal of multiple adenomas was carried out on February 26. Exploratory laparotomy on March 11 revealed multiple adenomas of the pancreas, and subtotal pancreatectomy was performed. On June 2, most of the remaining pancreas was removed. Previously, we have presented data which, in our opinion, definitely relate the neuronopathy in this patient to her hyperfunctioning pancreatic adenoma and not to other endocrine adenomas.[1]

In July, clinical examination revealed improvement. Although the patient's hands were still weak, paresthesia had disappeared. In January 1956, the patient reported that she was gaining weight and was now able to walk without crutches. The patient was next seen in May 1957, at which time remarkable improvement was evident and no weakness could be demonstrated clinically in the hands or feet. In October 1959, the patient reported that she had no disability in her hands or feet and that she was active as a physical education teacher.

Electromyographic examination on February 15, 1955, approximately three weeks after the onset of paresthesia in the hands and feet,

From the Sections of Physiology and Neurology, Mayo Clinic and Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.



Hyperinsulin neuronopathy after recovery of strength and bulk of muscles (May 1957). Action potentials of the hypothenar group of muscles evoked by electric stimuli of increasing strength applied percutaneously to the ulnar nerve at the elbow or at the wrist. Stimuli were single square wave pulses of 0.1 msec. at the elbow and 0.5 msec. at the wrist. Responses were recorded from cathode ray oscilloscope. Moment of stimulation is indicated by small "shock artifact" at arrows and is followed after a few milliseconds by the muscle action potential. Voltage of each stimulus is indicated above arrow. On the left, stimulation with 22 to 32 volts evokes a response of normal contour and latency (response to stimulation of low-threshold motor nerve fibers). On the right, greater voltages excite an additional response of longer latency (response to stimulation of high-threshold motor nerve fibers) superimposed on the low-threshold response. Time signal is 1,000 cps.

revealed evidence of denervation of skeletal muscles. Fibrillation, grade 2 to 3, was present in muscles in the left forearm, hand, and leg. No fasciculations were observed. Motor unit action potentials were greatly reduced in number but were of normal size and fired at a rapid rate during strong effort to contract the muscle. On March 9, the electromyogram was essentially the same, although the amount of fibrillation evidenced in the resting muscles had increased. Similar results were obtained on March 23. By this time, grade 2 fibrillation was present in both biceps brachii as well as in more distal muscles of the extremities.

In May 1957, nearly two years after pancreatectomy, there was no evidence of denervation. No definite fibrillation potentials were detected in the first dorsal interosseous, biceps brachii, and anterior tibial muscles. Rare fasciculations in the first dorsal interosseous and anterior tibial muscles were noted. Motor unit action potentials were essentially normal, with a slight or questionable reduction of number in the first dorsal interosseous and anterior tibial muscles. Measurements of the amplitude of the action potentials in the biceps brachii muscles (geometric mean of amplitudes over 100 μv.) gave values that were essentially the same as those obtained in March 1955. The mean amplitude was 330 μv. in March 1955 and 290 μv. in May 1957 (range of normal mean values, 250 to 450 μv.; $n = 72$ persons). On both dates, no action potential in 10 areas of the muscle exceeded 3.2 mv. and only one exceeded 1.6 mv. The strength-duration curve of the hypothenar muscles plotted on February 18, 1955, was typical of partial denervation. The chronaxy was greater than 10 msec. In May 1957, the strength-duration curve of the same muscle was in normal range and the chronaxy was 0.08 msec.

The most interesting and significant results were obtained from a study of conduction in the motor fibers of the ulnar and median nerves (see figure). The method employed was similar to that described by Hodes, Larrabee, and German.[4] The action potential of a muscle, evoked by stimulation of its nerve, is recorded by electrodes on the skin over the belly and tendon of the muscle. The size of the action potential is a measure of the number of muscle fibers that respond, while the latency of the response after nerve stimulation is largely the time for conduction of the nerve impulse from the point stimulated to the nerve endings and across the neuromuscular junctions. In February 1955, the amplitude of the action potential evoked in the left hypothenar muscles by maximal stimulation of the ulnar nerve was 0.6 mv., approximately 5% of average normal value (normal, 5.6 to 20.8 mv.; mean, 11.4 ± 0.29 mv.; $n = 103$), but the duration of the action potential was in the normal range. The action potential was essentially the same in amplitude and duration whether the

nerve was stimulated at the elbow or at the wrist. The speed of conduction in the proximal and distal parts of the functioning motor nerve fibers was normal. Conduction velocity between elbow and wrist in the ulnar nerve was 58 meters per second (normal, 47 to 73 meters per second; mean, 60 ± 0.4 meters per second; n = 188).

Similar results were obtained on March 9 and 23, 1955. In May 1957, several changes were observed. The magnitude of response of the hypothenar muscles was increased. Maximal stimulation of the ulnar nerve at the elbow evoked in these muscles an action potential of 2.8 mv., whereas stimulation at the wrist evoked an action potential of 5.4 mv. The duration of both action potentials was prolonged but was shorter when the stimulus was applied at the wrist than at the elbow; this indicated that the difference in amplitude of response to stimulation at elbow and wrist resulted from a greater degree of synchronization of the activity of the muscle fibers when the stimulus was applied at the wrist than when it was applied at the elbow. Conduction velocity of the fastest motor fibers (61 meters per second) remained in the normal range, but conduction velocity of other fibers was much slower than that observed in normal nerves.

More detailed examination of the response to stimulation of the ulnar nerve in May 1957 revealed that there were 2 different groups of motor fibers responding to the electric stimulus (see figure). The first was a group of fibers that had a normal, low threshold to electric stimulation and a normal conduction velocity. This group of fibers was similar in its characteristics to that which was functioning in February and March 1955, although in 1957 the amplitude of response of the hypothenar muscles after stimulation of this group of fibers was 4 to 5 times what it had been in February and March 1955. The second group of fibers had a high threshold to electric stimulation and a low conduction velocity. The latency of response to stimulation of these fibers was longer than that to stimulation of the fibers of the first group. No evidence was obtained that fibers of the second group were present at the time of the examinations in February and March 1955.

In 1957, when an electric stimulus was applied to the ulnar nerve at the elbow, fibers of the first group were maximally excited when 22 volts were applied for 0.1 msec. (see figure). Fibers in the second group began to respond when the stimulus was increased to 32 volts, but all the fibers did not respond until a voltage of 60 was reached. A similar phenomenon was observed in the median nerve.

COMMENT

For us, the most satisfactory explanation for the presence of two groups of motor fibers differing in threshold to electric stimulation and in conduction velocity is as follows: The group of fibers having a high threshold to electric stimulation and a low conduction velocity is composed of fibers that have regenerated from previously damaged axons and have not yet attained a normal diameter, excitability, and conduction velocity. The group of fibers having a low threshold to electric stimulation and a normal conduction velocity includes fibers that were not damaged by hyperinsulinism. However, the response to stimulation of this group of fibers was approximately 4 to 5 times as great in May 1957 as it was in February and March 1955. This could occur as the result of an increase in number of fibers in this group by maturation (with an increase in diameter, excitability, and conduction velocity) of some of the fibers that regenerated from previously damaged axons or by recovery of some fibers that may have been temporarily nonfunctioning but had not undergone wallerian degeneration during hyperinsulinism.

Some alternative explanations for the responses to electric stimulation observed in May 1957 must be considered. The presence of small-diameter motor fibers in the ulnar nerve might result from the sprouting of branches from otherwise unaffected axons rather than by regeneration of previously damaged axons. Evidence for the occurrence of sprouting in diseases that affect anterior horn cells has been presented by Wohlfart,[3] Coërs and Woolf,[5] and others. Evidence suggests that functioning sprouts arise principally from intramuscular portions of the axon. Causey and Hoffman[6] indicate that, while sprouting also occurs from the axons outside the muscle, few

of these branches ever mature. Therefore, no evidence exists that functioning sprouts would be present in the ulnar or median nerves at the points stimulated (elbow and wrist) in our study. That intramuscular sprouting could account for the findings after the patient has recovered from the effects of hyperinsulinism seems unlikely. It would not explain satisfactorily the difference in strength of electric stimulus required to excite the two groups of motor fibers in the ulnar and median nerves, since the sprouts would be branches of the parent axon and should respond to any stimulus that excited the parent axon. Thus, both the parent axon and its sprout would be excited at the same stimulus strength. There would be no difference in apparent threshold of the fast-conducting and slow-conducting branches. Should sprouting have occurred proximal to the point of stimulation of the nerve, a low-threshold stimulus, exciting the parent fiber, might excite the sprout through an axon reflex. It seems unlikely, therefore, that sprouting of previously undamaged axons can explain the occurrence of the high-threshold, slow-conducting fibers during recovery from hyperinsulinism. Additional evidence in support of this conclusion is the fact that, in amyotrophic lateral sclerosis and poliomyelitis, no group of high-threshold, slow-conducting fibers has been observed, although collateral sprouting has been demonstrated to occur in these diseases of the motor cell.[3,5] Marked slowing of conduction of some motor nerve fibers (below 40 meters per second in the ulnar nerve), such as that observed in the patient with hyperinsulinism, has not been noted in the latter diseases,[7,8] but does occur in chronic polyneuropathy[9] and after regeneration of injured nerves.[4]

Sprouting of collateral branches from intact neurons to innervate muscle fibers denervated by degeneration of their neurons has been suggested as one cause of enlargement of the motor unit action potentials and the appearance of large polyphasic potentials in the muscle in lower motor neuron disease. In spinal muscular atrophies, motor unit action potentials may be increased in amplitude many times the normal amplitude. No significant change in size of motor unit action potentials occurred with recovery of muscle strength in the patient with hyperinsulinism. None of the large polyphasic action potentials commonly seen in poliomyelitis were observed.

Another possibility which must be considered is that the long duration of the muscle action potential evoked by supramaximal electric stimuli applied to the nerve after recovery in hyperinsulinism was the result of repetitive firing of the low-threshold axons caused by the high intensity to which the stimulus was increased in order to evoke the late response. However, if this were the case, a greater amplitude and shorter duration of response would not be expected when the stimulus was applied at the wrist than when it was applied at the elbow. Furthermore, the intensity of stimulus employed in this study does not evoke repetitive responses in normal persons or in persons with amyotrophic lateral sclerosis or poliomyelitis.

The conclusion is reached that the high-threshold, long-latency component of the response to stimulation of the ulnar nerve after recovery from hyperinsulin neuronopathy represents the response of immature, small-diameter motor nerve fibers that have regenerated from previously damaged axons rather than by sprouting from undamaged axons. The observations give physiologic evidence for involvement of the peripheral nerves in this patient with hyperinsulin neuronopathy.

REFERENCES

1. Mulder, D. W., Bastron, J. A., and Lambert, E. H.: Hyperinsulin neuronopathy. Neurology 6:627, 1956.
2. Barris, R. W.: Pancreatic adenoma (hyperinsulinism) associated with neuromuscular disorders. Ann. Int. Med. 38:124, 1953.
3. Wohlfart, G.: Collateral regeneration from residual motor nerve fibers in amyotrophic lateral sclerosis. Neurology 7:124, 1957.
4. Hodes, R., Larrabee, M. G., and German, W.: The human electromyogram in response to nerve stimulation and the conduction velocity of motor axons; studies on normal and on injured peripheral nerves. Arch. Neurol. & Psychiat. 60:340, 1948.
5. Coers, C., and Woolf, A. L.: The Innervations of Muscle: A Biopsy Study. Springfield, Ill., Charles C Thomas, 1959.
6. Causey, G., and Hoffman, H.: Axon sprouting in partially deneurotized nerves. Brain 78:661, 1955.
7. Henriksen, J. D.: Conduction Velocity of Motor Nerves in Normal Subjects and Patients With Neuromuscular Disorders. Thesis, Graduate School, University of Minnesota, 1956.
8. Lambert, E. H., and Mulder, D. W.: Electromyographic studies in amyotrophic lateral sclerosis. Proc. Staff Meet., Mayo Clin. 32:441, 1957.
9. Electromyography and electric stimulation of peripheral nerves and muscle. In Clinical Examinations in Neurology, by members of the Sections of Neurology and the Section of Physiology, Mayo Clinic. Philadelphia, W. B. Saunders Co., 1956, pp. 287-317.

CASE REPORT

Vertebral artery insufficiency produced by cervical osteoarthritic spurs

Creighton A. Hardin, M.D., William P. Williamson, M.D., and A. Theodore Steegmann, M.D.

THE SYNDROME of basilar artery insufficiency has attracted recent widespread interest, particularly regarding the efficacy of anticoagulant therapy[1] versus surgical therapy.[2] In routine cerebral vascular accidents, Hutchinson and Yates[3] have stressed the frequency of vertebral artery stenosis or occlusion. Of their 48 cases, 19 had atheromatous narrowing and 3 total occlusion of one or both vertebral arteries. Attention was called to the fact that distortion of the vertebral artery was sometimes caused by changes in the bony spine from cervical spondylosis.

Tatlow and Banner[4] demonstrated radiographically on one cadaver, after injection of a barium solution into the vertebral arteries, that right lateral rotation of the head resulted in temporary occlusion of the right vertebral artery by an osteophyte.

In 203 vertebral angiograms accomplished by radial artery catheterization, Radner[5] noted lateral displacement of the vertebral artery by cervical osteophytes in only 2 instances. Coburn and Lewis[6] reported that hyperextension of the neck can cause temporary failure of filling of the vertebral artery and noted lateral displacement of the vertebral artery by osteoarthritic spurs.

On fresh cadavers, Primbs and Weber[7] demonstrated narrowing of the vertebral artery by arthritic bone changes. Although Kovacs[8] discussed vertebral artery compression by lipping and what he termed "widening of the uncinate process," he stressed its importance in the production of head and neck pain rather than vascular insufficiency.

Thus, attention has been called to narrowing of the lumen of the vertebral artery by lateral osteophytes and obliteration of the vessel by turning of the head, but we have found no report of therapy for vascular insufficiency by surgical removal of the bony spurs. For this reason, this single case report seems justified.

CASE REPORT

W.H., a 50-year-old white male traveling salesman, was first admitted to the Neurology Service at the University of Kansas Medical Center on August 27, 1958. He gave a history of peculiar attacks of three years' duration, each characterized by rather rapid onset of thick speech, staggering gait, hazy vision, and light-headedness. Each attack would last from twelve to forty-eight hours and would clear spontaneously. They varied in severity from mild ones, in which only his wife could note his thick speech, to severe ones, in which he could not walk a straight line. His attacks averaged about one a month, and he was unaware of any factor that would produce them.

His past history included a differential sensory trigeminal rhizotomy for trigeminal neuralgia in 1944, with residual numbness of the left lower jaw.

Neurologic examination revealed a slightly unsteady gait, mild nystagmus on right and left lateral gaze, and a Babinski response bilaterally but no other neurologic deficit except

From the Department of Surgery, Section of Neurological Surgery, and Section of Neurology, University of Kansas School of Medicine, Kansas City.

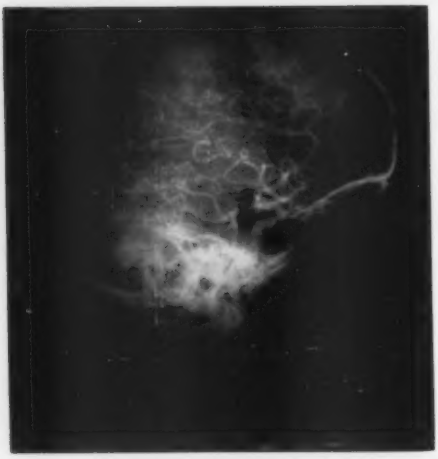


Fig. 1. Retrograde filling of the basilar artery after right carotid arteriograms suggesting vertebral insufficiency

Fig. 2. Right subclavian arteriogram showing filling of vertebral artery but with sharp angulation at C5 and C6

postoperative sensory impairment in the third division of the left fifth nerve.

Skull and chest roentgenograms were normal. Spinal puncture revealed an initial pressure of 120 mm., no cells, and a total protein of 38 mg. per cent. An electroencephalogram showed a moderately well organized record with paroxysmal irregular slowing and a few well defined high voltage spikes in the left temporal area.

The patient was dismissed without a positive diagnosis but was readmitted December 27, 1958, for further study. His attacks had continued unabated, and his abnormal neurologic signs persisted. On this occasion, it was noted that, when the patient's head was turned far to the right, his speech would become thick and his color pale, profuse perspiration occurred, and impending syncope demanded relief from this position.

A review of bilateral carotid arteriograms done elsewhere revealed retrograde filling of the basilar artery and its branches, suggesting vertebral artery insufficiency on the right side (Fig. 1). Cervical spine roentgenograms disclosed lateral osteoarthritic spurring between C4 and C5 and also between C5 and C6.

Bilateral percutaneous subclavian arteriograms done with 10 cc. of 50% Hypaque showed filling of the right vertebral artery with marked angulation and narrowing due to the arthritic spur between C5 and C6 and a lesser similar deformity between C4 and C5 (Fig. 2). The left vertebral artery could not be visualized.

A confirmatory study was then done by insertion of bilateral brachial catheters into the subclavian arteries under local anesthesia; 10 cc. of 20% Hypaque was used for each injection. The right vertebral artery was visualized with the head placed in an anteroposterior position; the procedure was repeated with the chin turned sharply to the right lateral position. The vertebral arteriogram in the anteroposterior position again showed sharp angulation from the spur (Fig. 3). The arteriogram taken with the head turned to the right showed a complete occlusion of the right vertebral artery at the C5-C6 level (Fig. 4). The left vertebral artery again was not visualized.

A decision was made to first explore the left neck in order to determine whether the nonvisualizing left vertebral artery represented a focal occlusion that could be corrected by an endarterectomy or a bypass graft. On January 9, 1959, under general anesthesia, the lower cervical area was explored through the bed of

Fig. 3. Right subclavian catheter arteriogram again confirming occlusive spur. (The white area seen in the center is an artifact.)

Fig. 4. Right subclavian catheter arteriogram with chin turned to right lateral position, completely occluding right vertebral artery

a subperiosteal resection of the inner one-half of the clavicle. No left vertebral artery arose from the subclavian artery. Sibson's fascia was cut, the pleura reflected laterally, and the aortic arch exposed. The origin of the left common carotid artery was identified, but there was no anomalous vertebral artery arising from the aortic arch.

Six days later, under endotracheal anesthesia in the supine position, the right vertebral artery in its canal was explored by an anterior approach between the carotid sheath and the trachea. An arthritic spur compressing the vertebral artery, thought to be at the C5-C6 level, was found and removed with a bone curette; the level was marked with a silver clip. Postoperative radiograms revealed that the lesser C4-C5 lesion had been removed by error.

The wound was reopened on January 22, and the larger spur was identified and removed. The bony mass narrowed the arterial lumen by one-half and was adherent to the arterial wall. Procaine was applied locally to the vessel wall to prevent arterial spasm. The postoperative course was uneventful, with no symptoms of vascular insufficiency, though a transient right twelfth nerve paresis occurred because of operative retraction of the hypoglossal nerve.

A percutaneous right subclavian arteriogram done on the fifth postoperative day revealed absence of the arthritic spurs and marked improvement in the vertebral artery deformity (Fig. 5). Rotation of the head to the right postoperatively failed to reproduce the preoperative symptoms. The patient has had no further attacks in the nine-month follow-up period, though the bilateral Babinski response persists.

DISCUSSION

The beautiful filling of the basilar artery on the right carotid arteriograms was strong presumptive evidence of vertebral artery insufficiency in this patient. This phenomenon was reported in 2 patients by van der Zwan[9] in 1954 and certainly indicated further investigation of the vertebral system.

Complete and thorough arteriographic studies are necessary to diagnose and select suitable cases for surgical correction. The reproduction

Fig. 5. Right postoperative arteriogram after vertebral canal decompression with removal of spur

of the vertebral artery occlusion by manipulation of the neck with the subclavian catheter in place for serial injections of radiopaque dye sharply localized the lesion that existed in this patient.

Thorough surgical exploration also disclosed congenital absence of the left vertebral artery. Daseler and Anson,[10] in reviewing the surgical anatomy of the subclavian artery, find that the vertebral artery arises from the subclavian in 91% of cases. Anomalous origins were described as left vertebral from aortic arch (2.46%), right vertebral from aortic arch (0.28%), and dual or accessory from aortic arch (0.72%). Congenital unilateral absence was not reported.

Lateral osteophytes occur as a degenerative change in the lateral intervertebral joints, first described by Luschka in 1858. These joints are mentioned in the literature under a surprising number of names, including joints of Luschka, uncovertebral joints, neurocentral joints, hemiarthroses intervertebral lateralis, and lateral interbody joints. Though Bovill and Drazek[11] deny the presence of these joints, Jackson[12] emphasizes the importance of their anatomy and remarks on their tendency to osteophyte production.

Although much emphasis has been placed on intervertebral foraminal narrowing by these osteophytes and their role in the production of radicular head and neck pain, especially in lower cervical spine, their possible role in the production of vertebral artery insufficiency has not been properly stressed. Schneider and Crosby[13] have recently reemphasized the significance of vascular impairment to the brain stem and cervical cord by mechanical distortion of the vertebral arteries. We join their plea for further investigation of the vertebral artery in patients with cervical spine pathology.

SUMMARY

A patient with basilar artery insufficiency due to congenital absence of one vertebral artery and compression of the opposite vertebral artery by osteoarthritic spurs is presented. Successful relief of symptoms was obtained by surgical excision of the offending osteophytes.

REFERENCES

1. Crawford, E. S., DeBakey, M. E., and Fields, W. S.: Roentgenographic diagnosis and surgical treatment of basilar artery insufficiency. J.A.M.A. 168:509, 1958.
2. Millikan, C. H., Siekert, R. G., and Whisnant, J. P.: Anticoagulant therapy in cerebral vascular disease —current status. J.A.M.A. 166:587, 1958.
3. Hutchinson, E. C., and Yates, P. O.: The cervical portion of the vertebral artery; a clinico-pathological study. Brain 79:319, 1956.
4. Tatlow, W. F. T., and Banner, H. G.: Syndrome of vertebral artery compression. Neurology 7:331, 1957.
5. Radner, S.: Vertebral angiography by catheterization. Acta radiol. supp. 87:1, 1951.
6. Lewis, R. C., and Coburn, D. F.: The vertebral artery. Missouri Med. 53:1059, 1956.
7. Primbs, A., and Weber, E.: Die Bedeutung des Verlaufes der Arteria vertabralis für die Pathogenese der zervikalen Syndrome; eine experimentell-anatomische Studie. Deutsche med. Wchnschr. 81:1800, 1956.
8. Kovacs, A.: Kephalgia e Subluxatione artic. cervicalis. Fortschr. Geb. Röntgenstrahlen 85:142, 1956.
9. van der Zwan, A.: Angiographic diagnosis of vertebral artery thrombosis. J. Neurol. Neurosurg. & Psychiat. 17:189, 1954.
10. Daseler, E. H., and Anson, B. J.: Surgical anatomy of the subclavian artery and its branches. Surg., Gynec. & Obst. 108:149, 1959.
11. Bovill, E. G., and Drazek, J. A.: An anatomic study of the cervical spine based on a clinical-roentgenologic concept of the etiology of brachialgia. Univ. Michigan M. Bull. 16:387, 1950.
12. Jackson, R.: The Cervical Syndrome. 2d ed. Springfield, Ill., Charles C Thomas, 1958.
13. Schneider, R. C., and Crosby, E. C.: Vascular insufficiency of brain stem and spinal cord in spinal trauma. Neurology 9:643, 1959.

Pathogenesis of cerebral vasospasm in hypertensive encephalopathy

II. The nature of increased irritability of smooth muscle of pial arterioles in renal hypertension

John S. Meyer, M.D., Arthur G. Waltz, M.D., and Fumio Gotoh, M.D.

In a previous communication,[1] a series of acute experiments were described which were designed to clarify the nature of the cerebral vasospasm that occurs in severe hypertension. In those experiments, the effects of sudden increases in intraluminal pressure were investigated. Moderate degrees of cerebral vasoconstriction were demonstrated to occur during rapid, severe increases in intraluminal arterial pressure. However, vasoconstriction was not considered to be sufficient to warrant the term "vasospasm" or to account for the cerebral symptoms that are seen in hypertensive encephalopathy. Nevertheless, intravenous injection of hypertensin, produced more intense pial arterial constriction.

The present series of experiments was designed to study effects of chronic renal hypertension on cats and monkeys; cranial windows for observation and photography of the pial vessels were used in a manner similar to that reported by Byrom[2] in the rat. The effects on pial blood flow and intracranial pressure of anemically and chemically induced hypotension were examined. The methods employed permitted analysis of 4 factors that might be responsible for cerebral vasoconstriction:

- Changes in intraluminal arterial pressure
- Circulating vasoconstrictor factor
- Brain swelling and compression of cerebral vessels
- Increased irritability of arterial smooth muscle.

Material and Methods

Attempts were made to induce renal hypertension in 12 Macacus rhesus monkeys and 5 cats. In an additional cat, spontaneous hypertension of nonrenal origin was studied; histologic examination showed normal kidneys. This animal is an additional example of spontaneously occurring hypertension in the cat, which has been reported.[3] The Goldblatt method[4] was used for producing renal hypertension in 6 monkeys. The technic of Page[5] was used in the remaining 6 monkeys and 5 cats.

The surgical technic consisted of endotracheal intubation after anesthesia induced by 30 mg. of Nembutal per kilogram of body weight given intravenously with 0.5 mg. of atropine. By aseptic technic, the right common carotid artery was ligated or closed with a small Crutchfield clamp.[6] Such clamping of one carotid artery permitted observations of the effects of renal hypertension on the normal and the ischemic cerebral circulation. Both kidneys were exposed and mobilized through bilateral, subcostal, transverse incisions. The left kidney was removed, and the right renal artery was constricted by means of a Salibi clamp (Fig. 1) until the pulsations were nearly obliterated. When the Page technic was used, the right kidney was wrapped in a sheath of sterile cellophane secured at the hilus with metal clips. The cellophane produced a con-

From the Departments of Neurology, Wayne State University College of Medicine, Detroit, and Detroit Receiving Hospital.
Dr. Gotoh is a Fellow of the Michigan Heart Association.
This work was supported by grants from the Michigan Heart Association, the National Institute of Neurological Diseases and Blindness, and the Research Corporation of Detroit Receiving Hospital and by contract NR 101-401 between the Office of Naval Research, Department of the Navy, and Wayne State University. Opinions expressed are those of the authors and do not necessarily represent those of the Department of the Navy.

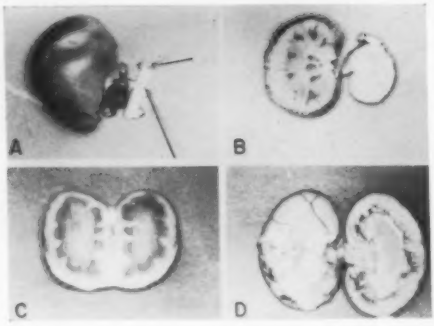


Fig. 1. Photographs of kidneys removed from 4 animals operated upon to produce experimental renal hypertension. [A] Right kidney removed at autopsy from a monkey with blood pressure of 240/180. Note Salibi clamp on renal artery. The pins have been inserted through the aorta. [B] Monkey in which a clamp had been placed on the renal artery of the left kidney (small kidney) and the right had been wrapped in cellophane. [C] Right kidney that had been wrapped in cellophane fifty-five days before removal from cat. [D] Cat kidney that had been wrapped in cellophane. The fibrous wall has been partially stripped.

stricting, perinephritic fibrous hull. All wounds were closed in layers, and the skin was sutured. The femoral artery was exposed through a short incision and a 21-gauge needle inserted. The blood pressure was recorded directly with a pressure transducer and ink-writer.[1]

In the early experiments, bilateral sterile Forbes windows made of stainless steel and glass[7,8] were screwed into the calvarium over both frontoparietal regions after resection of the dura. In later experiments, insertion of the windows was delayed until after the systolic blood pressure had risen to 140 mm. because the dura grew over the exposed pia after several weeks and obscured the pial vessels.

The pial circulation of both the normal and the ischemic hemisphere was observed and photographed repeatedly at magnifications of 56 and 80[1] before and after the development of renal hypertension. If the dura grew over the pial field and obscured the vessels, the windows were removed and reinserted over a different site. In several animals, the retinal vessels were also repeatedly observed with an ophthalmoscope and observations were noted on the protocols before and during hypertension.

The systolic blood pressure was measured daily with a sphygmomanometer connected to a pediatric blood pressure cuff wrapped around the lower abdomen; the point at which the femoral pulse disappeared, as determined by palpation, was recorded. At regular intervals of two weeks, and more frequently after the onset of hypertension, a needle was inserted into the femoral artery and the blood pressure was recorded directly through a small incision made in the skin. It was found that determinations of the systolic blood pressure made by palpation and those obtained by direct recording agreed within 10 mm. Hg.

All animals received daily injections of streptomycin, penicillin, and 5 mg. of desoxycorticosterone acetate (DOCA), with 1 tablespoonful of salt added to the drinking water each day. If hypertension resulted, any effects of removal and replacement of the DOCA and salt regimen on the blood pressure were noted.[9] Determinations of blood urea nitrogen were made once weekly in all animals by a micromethod with 0.2 cc. of blood (Dr. B. Zak, Department of Pathology, Wayne State University and Detroit Receiving Hospital, kindly made possible the blood urea nitrogen determinations by his laboratory). In 4 hypertensive animals, any effects on the pial vessels of reduction of blood pressure by means of the intravenous injection of 100 μg. of sodium nitroprusside[10,11] were noted and compared to the effects of hypotension induced by the intravenous injection of hexamethonium or the removal and replacement of venous blood.

In the cat with spontaneous hypertension, the pial blood flow and cerebrospinal fluid and blood pressures were continuously recorded while photographs were made of the pial vessels through the skull window. Pial blood flow was recorded with a thermistor, and the blood and cisternal cerebrospinal fluid pressures were recorded with pressure transducers and an ink-writing oscillograph.[1]

Uremia without hypertension was noted in 5 animals, and photographs of the pial circulation and ophthalmoscopic observations were made for comparison with those from the hy-

pertensive animals. The periods of observation of the latter varied from one to eight months. Autopsies were performed in all animals; any changes in the brain or viscera were noted, and representative sections of the brain were prepared for histologic observation.

RESULTS

Experiments were performed in 17 animals, 12 monkeys and 5 cats. Chronic hypertension with a systolic blood pressure in excess of 140 mm. Hg was induced in 6 monkeys and 3 cats, in excess of 170 mm. in 5 animals, and in excess of 210 mm. in 2 cats and 1 monkey. Only 2 of the hypertensive animals became uremic terminally, 1 after severe reduction of blood pressure by removal of venous blood, resulting in renal infarction. In 5 animals, uremia without hypertension was observed.

The Goldblatt and Page methods were both found satisfactory for producing hypertension. The Goldblatt method yielded results more rapidly, the blood pressure exceeding 210 mm. Hg in 1 animal five weeks after operation. However, the Page technic was more practical, since uremia occurred less frequently. Renal hypertension was always accompanied by marked diastolic hypertension, usually comparable to the rise of systolic pressure, so that pulse pressure remained small.

The daily injection of DOCA and the addition of salt to the diet did not appear to affect the course of the hypertension, nor did this method of causing salt retention make any observable change in the pial vessels. All animals received DOCA plus salt; however, 8 animals did not become hypertensive because operation failed to produce satisfactory renal ischemia. Withdrawal and replacement of DOCA in hypertensive animals or in those with beginning hypertension did not appear to alter the course of the disease.

It was arbitrarily decided to exclude from the hypertensive study any animals with blood urea nitrogen exceeding 45 mg. per cent because renal insufficiency itself may cause severe cerebral circulatory effects. However, the animals with uremia in the absence of hypertension were studied in a similar manner for comparison with the hypertensive group.

Hypertensive animals. *Changes in the pial circulation in chronic hypertension.* When the blood pressure exceeded approximately 160/110 mm. Hg, progressive constriction of the pial arterioles was noted to occur (Figs. 2 through 6). The degree of constriction correlated well with the degree of hypertension, that is, the higher the blood pressure, the greater was the degree of arteriolar constriction. In the monkey, constriction was diffuse from onset of its appearance (Figs. 5 and 6) but, in the cat, began as focal segmental narrowing (Figs. 7 and 8). The longer the duration of the hypertension, the more marked was the arteriolar constriction. For example, Figure 8A is a photograph of the pial circulation of a cat in which the blood pressure had become elevated to 210 mm. Hg ten days previously; only moderate segmental constriction was evident in the arterioles. The photograph in Figure 8B was taken after the sys-

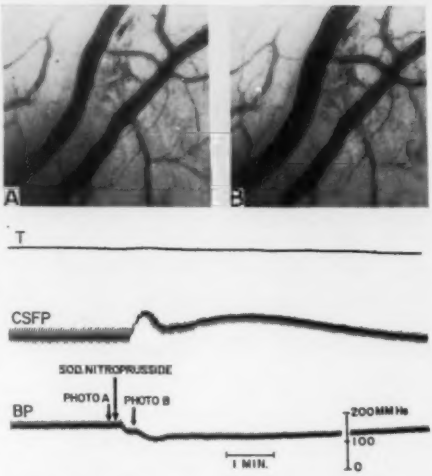


Fig. 2. Concurrent records showing the effect of intravenous injection of 100 μg. of sodium nitroprusside on the pial vessels [photos A and B], pial blood flow (T), cisternal pressure (CSFP), and carotid blood pressure (BP) of a cat with spontaneous hypertension. When photograph A was taken, at point marked A on the record, blood pressure was 175/145, large arteriole measured 200 μ. and side branch passing across the vein measured 44 μ. When photograph B was taken, at point marked B, pressure was 155/125, large arteriole measured 290 μ, and side branch measured 88 μ.

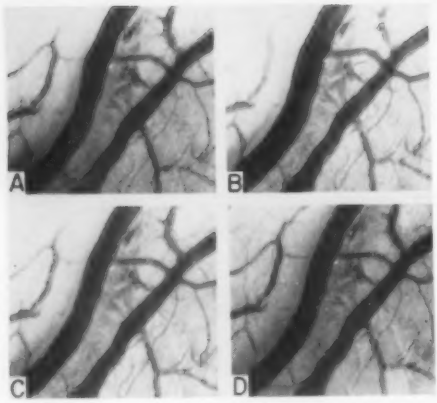


Fig. 3. Production of marked arterial dilation by sodium nitroprusside in a cat with chronic hypertension before blood pressure falls. [A] Pressure is 180/150, large arteriole measures 200 μ, and small one measures 70 μ. [B] Ten seconds after intravenous injection of 100 μg. of sodium nitroprusside, pressure remains at 180/150 but large arteriole now measures 250 μ and small arteriole 70 μ. [C] Three minutes later, pressure is 125/105 and arteriole is constricting, now measuring 210 μ. [D] Five minutes later, pressure has returned to 170/140 and arteriolar measurements are the same as in A.

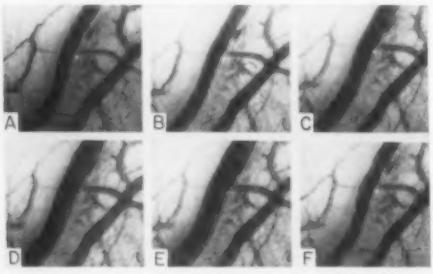


Fig. 4. Serial photographs showing the effect of removal of venous blood and clamping of thoracic aorta in a cat with spontaneous hypertension (same animal as in Figures 2 and 3. [A] Blood pressure is 180/150. [B] After withdrawal of 45 cc. of blood, pressure is 80/70 and marked arterial vasodilation begins. [C] After withdrawal of 48 cc., pressure is 65/60 and further dilation is evident. [D] After withdrawal of 55 cc., pressure is 55/45 and maximal dilation is seen. [E] Aortic clamp has been closed for eight seconds, and pressure is 100/75. [F] Sixty seconds after clamping of thoracic aorta, pressure is 145/140 and arterial constriction is already marked.

tolic blood pressure had remained elevated to 210 mm. for seventeen days; at this time, diffuse constriction of the arteriolar bed was sufficient to warrant the term "spasm." Brain swelling, pallor of the cortex, and a few perivascular hemorrhages were also present.

Brain swelling clearly preceded the arteriolar spasm and appeared to be an independent process, that is, arterial spasm was not essential for the appearance of brain swelling, nor did brain swelling cause "spasm" of the pial vessels by compression. At necropsy, the swelling was less marked on the side of the ligated carotid artery than in the hemisphere with intact circulation (Fig. 9). The theoretic basis for development of brain swelling in hypertensive encephalopathy has been discussed previously.[3] It appears that, when the systolic blood pressure is greatly increased, the rate of filtration in the arteriolar and capillary bed increases, since the increased intraluminal pressure in these small vessels exceeds the colloid osmotic pressure. Perivascular hemorrhages were seen only in those animals in which the systolic blood pressure was elevated above 200 mm. for two or more weeks.

Occasionally, in aged cats, spontaneous hypertension was noted with blood pressure in excess of 175/125 mm. Hg. In such animals, the pial vessels regularly show segmental constriction.[3] The pattern of the changes in the pial vessels with renal hypertension was similar to that seen in cats with spontaneous hypertension (Figs. 2 through 4).

Renal excretory insufficiency did not appear to be responsible for the hypertensive arteriolar spasm because the blood urea nitrogen was normal during its development in 3 cats and 3 monkeys. The degree of spasm of the cerebral vessels was not apparently influenced by the addition or subtraction of dietary salt or the use of DOCA. Arteriolar spasm was present bilaterally, in both the hemisphere rendered ischemic by ligation of the carotid artery and the other with intact blood supply. However, in some experiments, such as shown in Figure 6, the arteriolar spasm was considered to be less marked on the side of the ligated carotid artery. In general, the appearance of the pial vessels in hypertension correlated well with the appearance of those of the retina.

In cats with severe renal hypertension, evidence of increased irritability of the small arterioles was found, as shown in Figure 7. Photographs A and B were both taken in an animal with a measured blood pressure of 260/180 and in which symptoms of hypertensive encephalopathy were present. Photograph A was taken before removal of the window. Areas of segmental arteriolar spasm were visible, appearing as waist-like constrictions similar to those described by Byrom.[2] The window was removed to see if pressure against it was the cause of the spasm. The mechanical pressure of the window against the vessels during removal resulted in the appearance of many more segmental and diffuse constrictions of arterioles. Earlier experiences in many hundreds of experiments in which similar or more severe mechanical stimulation of the pial vessels occurred has never resulted in such a marked degree of arteriolar spasm. Furthermore, such marked arterial spasm has never occurred in experiments in which acute mechanical hypertension of comparable levels was obtained by clamping of the thoracic aorta.[1]

Photographs were taken before and after temporary removal of the skull windows in several animals with hypertensive spasm in order to decide whether direct pressure of the pial vessels against the windows was a contributing factor. In all cases, the spasm was not relieved by removal of the windows and was clearly not a pressure artifact. In a few animals in which severe hypertension persisted for many weeks, serial photographs showed increased tortuosity of the small arterioles.

Effects of lowering of the blood pressure in hypertension by anemia or hypotensive drugs. In the animals with severe hypertension, numerous experiments were devoted to restoring the blood pressure to normotensive levels by the removal of venous blood or the use of the hypotensive agents hexamethonium and sodium nitroprusside. A critical level of blood pressure above which "spasm" occurred and below which "spasm" was absent was not found. During the induction of hypotension, such as produced by the withdrawal of 60 cc. of venous blood from the femoral vein, the femoral blood pressure was continuously recorded and repeated photographs were made

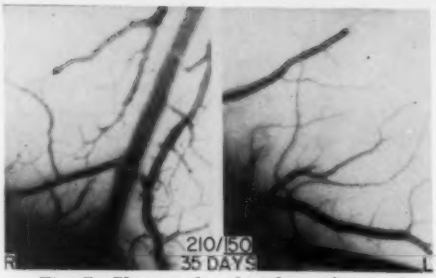


Fig. 5. Photographs of pial circulation of a monkey in which renal hypertension had been induced by operation thirty-five days earlier. Blood pressure measured 210/150 at the time the photographs were made. R is a photo of the right hemisphere, L of the left. Large arteriole in R measures 150 μ. Diffuse arteriolar constriction is less marked on the right; right carotid artery had been ligated.

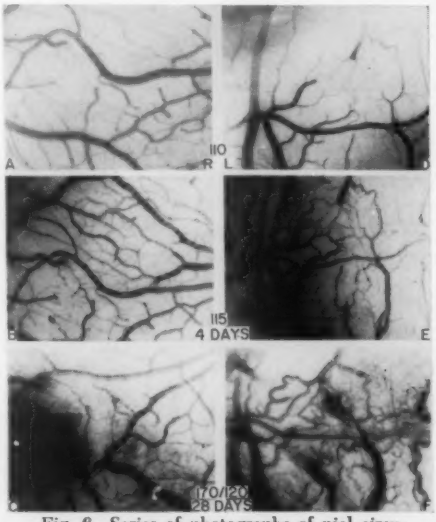


Fig. 6. Series of photographs of pial circulation of a monkey before and after development of moderate renal hypertension. Photographic fields are comparable but at slightly different magnifications. A, B, and C are photos of right hemisphere, which was ischemic. D, E, and F are photos of hemisphere with intact circulation. Transverse artery in D measures 100 μ. A and D were taken on the day of renal surgery, when systolic blood pressure was 110; B and E were taken four days later, when pressure was 115. C and F were taken on the twenty-eighth day, when pressure was 170/120. Diffuse arteriolar constriction is greater in the left hemisphere with intact circulation.

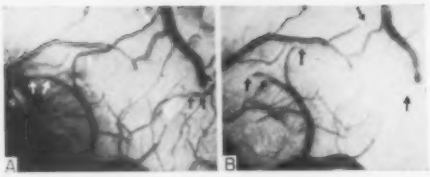


Fig. 7. Increased irritability of arteriolar smooth muscle in a cat with severe renal hypertension. [A] Photograph of pial vessels of left hemisphere (circulation intact) with window in place. Blood pressure is 260/180. Black arrows show segmental spasm; white arrows show arterioles in which spasm was produced by mechanical stimulation in B. After removal of window and gentle pressure against the vessels. Black arrows indicate intense spasm. Pressure is still 260/180.

of the pial circulation. The pial circulations of both the normal and the ischemic hemisphere reacted in a similar manner. During the removal of venous blood in animals with pressures above 200 mm., the first discernible arteriolar dilation appeared as the pressure fell to 110 mm. Hg and, at 80 mm., dilation was marked. When venous blood was slowly replaced, the vessels began to constrict when the pressure returned to 120 mm. and continued to do so until the entire volume had been replaced (Fig. 4). It was clear, however, that the intraluminal pressure plays an important part in the spasm of chronic hypertension because clamping of the descending aorta after the removal of venous blood, and before its replacement, resulted in marked arterial constriction (Fig. 4E and F).

Intravenous injection of sodium nitroprusside in animals with severe hypertension also produced marked dilation of the constricted pial arterioles before the blood pressure began to fall (Fig. 2). This was accompanied by a slight increase in pial blood flow and an increase in cerebrospinal fluid pressure. As the sodium nitroprusside was excreted, the pial arterioles began to constrict before the blood pressure had risen to resting levels (Fig. 3). The dilation amounted to as much as 100% or more in vessels of 80 to 100 μ (Fig. 2).

Hexamethonium caused changes comparable to those seen with anemically induced hypotension—progressive arteriolar dilation beginning when the blood pressure had fallen below 130 to 150 mm. Hg. As in anemically induced hypertension, there did not appear to be a critical level of blood pressure above which spasm appeared and below which it was absent.

"Clinical" signs of hypertensive encephalopathy. Although marked changes in the pial vessels occurred in all hypertensive animals, in only one animal, a cat, could neurologic signs be definitely attributed to hypertensive encephalopathy without uremia. The protocol of this animal will be briefly summarized because the pattern of circulatory events is representative of all the animals that became hypertensive.

The blood pressure before surgery (Page technic) was 100/80. Twenty-eight days after surgery, the systolic blood pressure was 155 mm. Eighty-three days after surgery, the systolic blood pressure was 230 mm. by palpation. The pupils were dilated and failed to react to light. The ratio of arteries to veins in the retina was 1:3; normal is 1:2. The brain appeared swollen and pale, with narrowing of the pial arterioles similar to that seen in the retina. The blood urea nitrogen was 33 mg. per cent. Ninety days after surgery, directly recorded blood pressure was 260/80; the pupils remained dilated and fixed to light, and weakness of the legs and disturbance of gait were seen. Retinal and vitreous hemor-

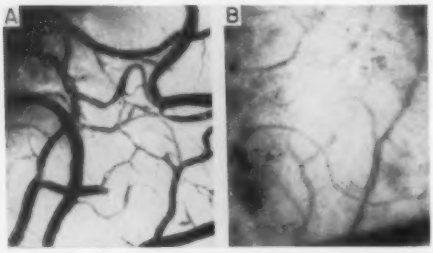


Fig. 8. Progressive arteriolar spasm in a cat with renal hypertension. [A] Photograph of pial circulation taken when systolic blood pressure had been 210 for ten days. There is moderate segmental constriction. [B] Photograph taken when systolic pressure had been 210 for seventeen days; marked and diffuse constriction, brain swelling, and perivascular hemorrhages are present.

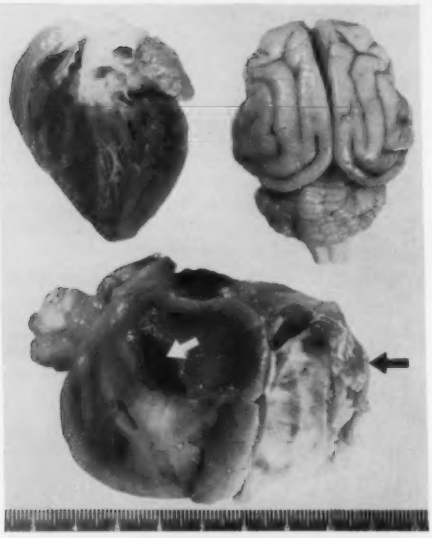


Fig. 9. Appearance of the brain, heart, and kidney in a cat dying of severe hypertension and hypertensive encephalopathy. Blood pressure was 260/180 before death. Brain is diffusely swollen and pale; swelling is greater in the left hemisphere (intact circulation) than in the right. Heart shows marked left ventricular hypertrophy. Left kidney had been removed and right kidney wrapped in cellophane some months before. Black arrow indicates thick fibrous hull and cellophane around hypertrophied kidney. White arrow indicates a parenchymatous hemorrhage that occurred after blood pressure was transiently lowered by removal and replacement of 80 cc. of venous blood.

rhages were noted in both eyes, and the retinal ratio of arteries to veins was 1:4. The brain beneath the skull windows appeared to be swollen, pale, and yellowish, with recent and old ball-shaped perivascular hemorrhages around the pial vessels. Addition of salt to the drinking water and daily intramuscular injection of DOCA did not influence the course of the hypertension. Blood urea nitrogen determinations remained normal until the blood pressure was reduced by removal and replacement of venous blood while the pial vessels were photographed. This caused infarction of the remaining kidney followed by a rise in blood urea nitrogen, which reached 170 mg. per cent at the time of death. At autopsy, the heart was greatly enlarged, the left ventricle being 1 cm. thick (Fig. 9). Moderate pericardial effusion was noted, and the lungs were congested. The brain was swollen, particularly over the left hemisphere; the right carotid artery had been ligated (Fig. 9). The remaining kidney was greatly hypertrophied and surrounded by a thick fibrous capsule. Linear hemorrhages were present in the parenchyma, which appeared pale (Fig. 9). In animals with longstanding hypertension, hypertrophy of the left ventricle of he heart similar to that shown in Figure 9 was a constant finding.

Uremic encephalopathy. All the uremic animals had neurologic symptoms, including nausea, vomiting, lethargy, drowsiness, coma, ataxia, vertical and lateral nystagmus, paresis, myoclonic jerks, excessive salivation, dilated pupils, and retinal and vitreous hemorrhages. The brain beneath the skull windows appeared pale and swollen, with moderate narrowing of pial arterioles and veins (Fig. 10). In some animals, this was probably due in part to hypotension (blood pressure of 70 to 100

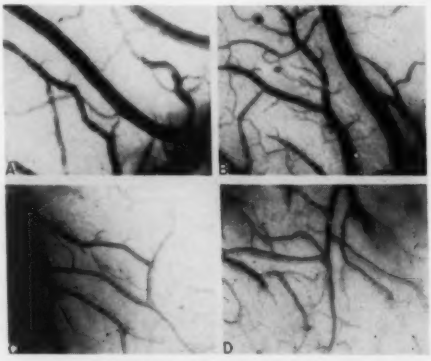


Fig. 10. Pial circulation in uremia. A is a photograph of the right hemisphere and B of the left in a cat with a systolic blood pressure of 120 and a blood urea nitrogen of 170 mg. per cent. Large arteriole measures 100 μ. Note perivenous and periarterial hemorrhages in B. C is a photo of the right hemisphere and D of the left in a cat with a systolic pressure of 80 and a blood urea nitrogen of 150 mg. per cent. Main trunk of arteriole in D measures 75 μ. In all photographs, the brain is pale and swollen.

mm.), which was present terminally in all animals. Arteriolar spasm was never seen in uremia in the absence of hypertension. Perivascular hemorrhages in the brain were seen through the skull windows and were also noted in the retina in uremic animals that had never been hypertensive (Fig. 7B). At necropsy, most of these animals showed pleural, peritoneal, and pericardial effusions, hemorrhagic pericarditis, hemorrhagic enteritis, and anasarca. The cause of the renal failure was invariably renal ischemia and infarction (Figs. 1 and 9).

DISCUSSION

The cause of cerebral arteriolar constriction in chronic hypertension has been studied in monkeys and cats. Only 1 cat had spontaneous hypertension of nonrenal origin; in the others, renal hypertension was produced by either the Goldblatt or Page technic in 60% of the animals operated upon. The main cause of operative failure was uremia, which developed in 5 animals. Serial photographs of the pial circulation permitted correlation of the level of blood pressure with the appearance of pial arteriolar constriction. Separate studies of 5 animals that became uremic without hypertension were made for comparison with the hypertensive group.

No definite and critical level of blood pressure above which arteriolar constriction appears was found, but, in general, when the blood pressure reaches 160/110 mm. Hg, progressive arteriolar constriction appears. Constriction is most evident in the small arterioles of 40 to 100 μ in internal diameter, although larger arterioles participate. Hypertensive arteriolar constriction begins segmentally in the cat and is similar to that reported in the rat[2] but is diffuse from onset in the monkey. The higher the blood pressure and the longer the duration of the hypertension, the more marked becomes the arteriolar spasm. When the systolic blood pressure remains in excess of 200 mm. Hg for three weeks and is accompanied by a proportionate rise in diastolic pressure, arterial spasm becomes diffuse and perivascular hemorrhages commonly appear. Brain swelling precedes the arteriolar spasm and is a direct effect of increased intraluminal pressure resulting in increased filtration from the vascular bed. Symptoms due to hypertensive encephalopathy, such as dilated and fixed pupils, gait disturbance, and retinal hemorrhages, were present in only 1 animal but correlated well with observations of the pial vessels. In this animal, the arteriolospasm and brain swelling were more marked than in any other experiment.

Ligation of one carotid artery before development of hypertension did not entirely protect the ischemic hemisphere from brain swelling or arteriolar spasm, but, in all instances, the brain edema and occasionally the arteriolar spasm were less marked in the ischemic hemisphere than in the one with intact blood supply. Presumably, this is because ligation of the carotid artery reduces the intraluminal pressure in its territory of supply.

The following factors must be considered in the mechanism of hypertensive cerebral arteriolar spasm.

Increase in intraluminal pressure appears to be an important but not the sole factor responsible for spasm. An approximate but not an exact correlation exists between the level of blood pressure and the appearance of cerebral arteriolar constriction. If intraluminal pressure were the only factor, closer correlation might be expected. For example, intravenous injection of sodium nitroprusside caused marked arteriolar dilation before any fall in blood pressure occurred, while removal of venous blood caused marked dilation only after the blood pressure had been reduced to very low levels (80 mm. Hg). The response to hypotension caused by the intravenous injection of hexamethonium was in between these extremes. Furthermore, it has been shown previously that the same degree of spasm seen in renal hypertension cannot be achieved by elevating blood pressure to comparable levels by purely mechanical means.[1]

A circulatory vasoconstrictor factor appears to play an important role because arterial constriction increased with time while the blood pressure remained elevated at a fixed level. Furthermore, spasm appeared in the distribution of a vessel that had been ligated, which reduces the intraluminal arterial pressure in that region. In addition, clamping of the descending aorta with the production of marked hypertension does not cause cerebral arteriolar

spasm in normal animals but does produce such spasm in hypertensive animals rendered normotensive by blood loss. Finally, intravenous injection of sodium nitroprusside resulted in sudden relaxation of arterial spasm before blood pressure fell, suggesting the inhibition of a pharmacologic factor. Such a circulating vasoconstrictor factor is present with experimental renal hypertension.[1, 12–14]

Brain swelling with vascular compression played no role in the production of arteriolar constriction, since it was present whether the skull was closed or opened by removal of the windows. It is possible that, in terminal hypertensive encephalopathy, brain swelling eventually causes vascular compression.[1,15,17]

Increased irritability of cerebral arterial smooth muscle can be demonstrated to be present in severe renal hypertension, since light mechanical stimulation results in marked segmental arterial constriction not seen in normotensive animals even with stimulation of a much coarser nature. It is probable that this increased irritability of cerebral arterial smooth muscle results from a specific pharmacologic effect of a circulatory vasoconstrictor factor present in renal hypertension.

In uremic encephalopathy, damage to cerebral vessels occurs in the absence of hypertension, resulting in brain swelling and perivascular hemorrhages. Presumably, in renal excretory insufficiency, a circulating toxin accumulates which causes arteriolonecrosis.

CONCLUSIONS

In experimental renal hypertension in the cat and monkey and in spontaneously occurring hypertension in the cat, cerebral arteriolar constriction and spasm result from a circulating vasoconstrictor factor that renders the smooth muscle of the arteriolar wall of cerebral vessels increasingly irritable, so that they respond to a normal or raised intraluminal pressure by excessive constriction. This excessive "Bayliss effect"[16] can be counteracted by lowering of the blood pressure. The most effective method is by intravenous injection of sodium nitroprusside, which has a direct paralytic effect on the smooth muscle of small arteries and counteracts the effect of any circulating vasoconstrictor factor while lowering the blood pressure. Since the arterioles in the territory of an occluded cerebral vessel constrict in severe hypertension, the collateral circulation is reduced and the territory supplied by an occluded vessel may be rendered more ischemic.

Technical assistance for this study was provided by Mr. Peter Miller. Dr. James Landers kindly reviewed the histologic sections of the brain, eye, and kidneys. Unquestionable fibrinoid necrosis of arterioles (focal arteriolar necrosis) was found in only one animal (a monkey) with longstanding renal hypertension.

REFERENCES

1. Meyer, J. S., Waltz, A. G., and Gotoh, F.: Pathogenesis of cerebral vasospasm in hypertensive encephalopathy. I. Effects of acute increases in intraluminal blood pressure on pial blood flow. Neurology 10:735, 1960.
2. Byrom, F. B.: The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension; experimental evidence from the hypertensive rat. Lancet 2:201, 1954.
3. Meyer, J. S.: Circulatory changes following vascular occlusion in occlusive cerebrovascular disease. In Fields, W. S., ed.: Symposium on Cerebral Vascular Disease. Springfield, Ill., Charles C Thomas. In press, 1960.
4. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on experimental hypertension. 1. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J. Exper. Med. 59:374, 1934.
5. Page, I. H.: A method for producing persistent hypertension by cellophane. Science 89:273, 1939.
6. Crutchfield, W. G.: Instruments for use in the treatment of certain intracranial vascular lesions. J. Neurosurg. 16:471, 1959.
7. Forbes, H. S., Nason, G. I., and Wortman, R. C.: Cerebral circulation; vasodilation in the pia following stimulation of the vagus, aortic and carotid sinus nerves. Arch. Neurol. & Psychiat. 37:334, 1937.
8. Meyer, J. S.: Circulatory and functional changes following middle cerebral artery occlusion in the monkey. J. Neurosurg. 15:657, 1958.
9. Frieden, J., Stamler, J., Hwary, W., Kuramoto, K. and Katz, L. N.: Effect of chronic salt depletion on blood pressure of renal hypertensive dogs. Am. J. Physiol. 168:500, 1952.
10. Gifford, R. W.: Current practices in general medicine. 7. Treatment of hypertensive emergencies including use of sodium nitroprusside. Proc. Staff Meet. Mayo Clin. 34:387, 1959.
11. Page, I. H., Corcoran, A. C., Dustan, H. P., and Koppanyi, T.: Cardiovascular action of sodium nitroprusside in animals and hypertensive patients. Circulation 11:188, 1955.
12. Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F., Munoz, J. M., and Taquini, A. C.: Renal Hypertension. Springfield, Ill., Charles C Thomas, 1946.
13. Page, I. H., and Corcoran, A. C.: Experimental Renal Hypertension. Springfield, Ill., Charles C Thomas, 1948.
14. Tigerstedt, R., and Bergman, P. G.: The kidneys and the circulation. Acta physiol. scandinav. 7-8:223, 1897-1898.
15. Cushing, H.: Some experimental and clinical observations concerning states of increased intracranial tension. Am. J. M. Sc. 124:375, 1902.
16. Bayliss, W. M.: On the local reaction of the arterial wall to changes of internal pressure. J. Physiol. 28: 220, 1902.
17. Wolff, H. G., and Blumgart, H. C.: The cerebral circulation. VI. The effect of normal and of increased intracranial cerebrospinal fluid pressure on the velocity of intracranial blood flow. Arch. Neurol. & Psychiat. 21:795, 1929.

Restless legs syndrome

K. A. Ekbom, M.D.

In 1944, I described an old, almost completely ignored syndrome, which I have denoted "restless legs."[1-8] Its clinical features are simple and easily recognized. The syndrome is so common and causes such suffering that it should be known to every physician. The descriptions given in the textbooks are, with few exceptions, sparse and partly inaccurate. I therefore intend to give a survey of this syndrome, based on 175 personal cases, as well as an account of some recent observations.

HISTORY

The oldest hitherto known description of the syndrome was found by Critchley,[9] who wrote:

"Few medical men know that Ekbom's syndrome was graphically described in the 17th century by that great clinical neurologist, Thomas Willis. In 1695, he wrote: 'Wherefore to some, when being a Bed they betake themselves to sleep, presently in the Arms and Leggs, Leapings and Contractions of the Tendons, and so great a Restlessness and Tossings of their Members ensue, that the diseased are no more able to sleep, than if they were in a Place of the greatest Torture.' "

Actually, this description is of even earlier date. It is found in the first edition of Willis' book,[10] published in 1685. Critchley quoted the second edition, printed in 1695. The next oldest known description is that of Wittmaack[11] from 1861. He devoted one page to an account of "die von den älteren Aerzten so genannte *Anxietas tibiarum*." It can be inferred that still earlier descriptions of this condition are to be found, but I have been unable to trace them. Wittmaack regarded anxietas tibiarum as a common symptom of hysteria.

Another early description was given by George M. Beard[12] in his book on neurasthenia:

"Fidgetiness and nervousness, inability to keep still—a sensation that amounts to pain—is sometimes unspeakably distressing. When the legs feel this way, the sufferer must get up and walk or run, even though he be debilitated and is made worse by severe exercise." The complaints were interpreted as "one of the myriad results of Spinal irritation."

Oppenheim[13] in his *Lehrbuch der Nervenkrankheiten* writes in the chapter on neurasthenia:

"Eine besondere Art subjektiver Empfindungsstörungen ist die Unruhe in den Beinen; sie kann zu einem quälenden Übel werden, Jahre und Dezennien bestehen und sich vererben resp. familiär auftreten. In Oppenheims Beobachtungen spielte das psychische Moment eine grosse Rolle."

The symptoms were thus interpreted as "hysterical" or "neurasthenic" and were accorded little interest.

In 1940, Mussio-Fournier and Rawak[14] reported a case of a syndrome consisting of pruritis, urticaria, and "a hyperkinesis of the lower extremities caused by paresthesias appearing during rest." The patient's mother and a sister had the same symptoms. Allison,[15] in 1943, gave a brief account of "a common minor ailment," which he denoted "leg jitters."

Since 1945, a number of reports on restless legs have been published. The most comprehensive publication is the well-written thesis of Jolivet,[16] inspired by Bonduelle. On broad lines, it can be said that nothing essentially new has been forthcoming. An important exception is Ask-Upmark's[17,18] and Nordlander's[19-21] observations of restless legs in anemia.

CLINICAL FEATURES

The salient symptom is peculiar creeping or crawling sensations most frequently localized to the lower leg, between the knee and ankle. They are fairly often present in the thigh as well and, sometimes, in the feet. Oc-

From the Department of Neurology, University Hospital, Uppsala, Sweden.

casionally, they are confined to the knees or feet. As a rule, the sensations are bilateral and symmetric, but a preponderance on one side may occur. In certain cases, a creeping sensation is felt alternately in the right and left leg but not in both at once. Involvement of the arms, but seldom the hands, may occur but is less severe and less common than that of the legs. The creeping sensations are not felt in the skin but deep inside, in the muscles or "bones."

The patients describe their sensations in a variety of ways, for example as something creeping, pulling, or stretching in their legs. The legs are so restless that they cannot be kept still. Graphic descriptions are sometimes heard, such as "It feels as if my whole leg was full of small worms" or "as if ants were running up and down in my bones," or "It feels like an internal itch." Many patients spontaneously use the expression "creeping sensation," but even intelligent patients often have difficulty in describing their symptoms. This is evidently due to the fact that the sensations do not resemble any known phenomenon that can be used as a comparison. For instance, they are not the same as those felt when a leg "goes to sleep." All the patients are, however, in agreement on two points: first, that, as long as the sensations last, it is impossible to keep their legs still, and, second, that the condition is exceedingly unpleasant. "It is a diabolical feeling." "I would not wish it on my worst enemy." "It spoils my whole life." "It is worse than any ordinary illness." Severe creeping sensations can produce general irritation or despair. "I get so angry that I swear" was the statement of a soldier. An otherwise well-balanced hospital nurse said: "I get so hysterical that I weep."

The creeping sensations in the arms are of exactly the same kind as those in the legs. They should not be confused with acroparesthesias, as they sometimes are.

Some patients speak of pain, but, on careful questioning, they generally admit that it is a matter of discomfort rather than of actual pain. However, in certain cases, true pain does, in fact, occur as a dull ache of slight to moderate intensity. As a rule, a patient with pain has creeping sensations as well, either concurrently with the pain or alternating with it. In some cases, the aching occurs alone, without creeping sensations.

The cases of restless legs may be divided into two groups, one in which the salient symptoms is creeping sensations and another smaller group that usually suffers pain. The present paper deals chiefly with the former group.

The most characteristic feature is not, however, the quality and localization of the sensations but the way in which they appear. Thus, they appear only when the limbs are at rest and are relieved by movement. They are almost invariably worse in the evening and at night.

In the daytime, the discomforts may disappear completely but often start when the patients have to sit still for any length of time, especially in the evening, and when they are tired. The sensations are worst on train journeys and at lectures, the theater, and movies. In some cases, the sensations occur only during boring films. Others are forced to leave even the most exciting performance. Some patients state that they never have a moment's peace. They can never sink into an armchair and relax. They cannot sit still at a bridge table or a dinner party. Their discomforts force them to walk up and down constantly, "like a lost soul," as one young woman said. However, most patients regard the creeping sensations during the daytime as only a minor discomfort. They do not become unbearable until the patients have gone to bed.

The creeping sensations start a short time (five to thirty minutes, sometimes more) after the patient gets into bed. In mild cases, they soon cease. In moderately severe cases, they last for some hours. In the severest cases, they persist, with interruptions, until 3, 4, or 5 a.m. or even longer. However, as a rule—even in extremely severe cases—they finally cease, so that the tormented patient gets at least one or two hours' sleep in the morning.

When the creeping sensations start, it is impossible to keep the legs still. Only in the mildest cases can the patients go to sleep despite the discomfort. Otherwise, they lie kicking or moving their legs around or massaging them. They often have to get up and walk,

"like a caged bear," to quote one of my patients, or they go into the kitchen and get something to eat. Others sit and smoke, knit, read, or play patience, kicking all the time. One middle-aged woman in my series used to dance the Charleston in her bedroom.

After a time ranging from a few minutes to an hour or more, the creeping sensations cease and the patient returns to bed. He may fall asleep. Often, however, the sensations reappear after an interval, and the patient has to get up and wander around again. This may be repeated many times during the night. One woman told me that she had to keep moving for half an hour. The creeping sensations soon stopped when she was walking but returned as soon as she got into bed. If, on the other hand, she kept moving for half an hour, the sensations ceased long enough for her to fall asleep. Even when the patients finally go to sleep, they may be awakened again by their discomforts. Others do not wake up but kick in their sleep, often to such an extent that the spouse is kept awake.

Restless legs are an important cause of severe insomnia. It is usually claimed that insomniacs sleep more than they actually believe. I have hospitalized several patients with restless legs for observation, and they have wandered up and down the corridors at night. There is, in fact, no doubt that these patients sleep just as badly as they say. It is not surprising that many patients complain bitterly about their ailment: "It is so dreadful that I scarcely dare to go to bed."

Heat and cold have no constant effect. Most patients do not like heat. The discomforts sometimes increase in patients obliged to sleep in their clothes, for example, soldiers. Certain patients stick their legs out of the blankets or pour cold water over them. One man in my series used to walk barefoot in the snow on his balcony. Some, on the other hand, find heat comforting and sleep with socks on their feet or with a hot-water bottle. Others find a hot bath helpful. Several patients have told me that the discomforts disappear when they have fever. One woman, for instance, stated that the creeping sensations never appeared when she had a temperature of 39° C. or above, whereas 38° C. was not sufficient to prevent them. Lying with the legs raised is seldom helpful.

Psychic factors are of some importance. Some patients experience creeping sensations during films, television programs, and lectures only when they are boring. Neurotics often complain bitterly— and apparently in an exaggerated way—about a whole series of symptoms, of which restless legs may be one. However, the majority of my patients have been calm, well-balanced persons without mental disturbances. A tendency exists to belittle symptoms of the type of restless legs. They are dismissed as "psychogenic" or "nervous." Many patients state that they are ashamed to talk about their discomforts to other persons. As a rule, this only results in their being laughed at. They are touchingly grateful at being taken seriously. One of my patients stated that his wife used to say to him: "Keep your legs still; it's only imagination." During pregnancy, she also had creeping sensations in her legs. She then apologized to her husband and said, "Now I know how dreadful it feels."

The creeping sensations are the most regularly occurring clinical feature. As already mentioned, some patients have pain in the legs, which may also feel tired, heavy, and weak. The feet or lower legs are often cold. A few patients in my series complained of burning sensations in the soles of their feet at night or a cramp in the calf. I do not include the two last-mentioned symptoms in the syndrome of restless legs even though it is possible that some relation exists.

PHYSICAL SIGNS

No neurologic abnormalities have been demonstrated. Several patients in my series had iron deficiency with or without anemia. Of 77 unselected severe cases, 19 had a serum iron level below 60 μg. per 100 cc.

COURSE AND INTENSITY

All transitions from mild to exceedingly severe cases are found. The former have slight, occasional creeping sensations of short duration, generally in the evening after a tiring day or on long journeys. The nights may be entirely free from discomfort. In the severest cases, the creeping sensations persist for prac-

tically the whole night, night after night, year after year, often for decades. As a rule, the history is of many years' duration, with better and worse periods. Long asymptomatic intervals may occur. Mild cases may become severe and vice versa. Women generally notice an exacerbation during pregnancy. The ailment may have its onset at any age. Some patients state that their sensations appeared before they were 10 years of age. In my series, the highest age at onset was 82 years.

The mild cases are rather common. Thus, I found such symptoms in 5% of a "normal series" consisting of 500 healthy subjects. The incidence was about the same in men and women, with no preponderance in any particular age group.[2] Such persons do not seek medical advice and, as a rule, are not greatly inconvenienced by their symptoms.

The moderately severe and severe cases are less common than the mild ones but are by no means rare. Thus, during a fifteen-year period, I have collected 175 typical cases, many of them truly severe. Of these patients, 72 were men and 103 women. Nearly all of them consulted me because of their leg discomforts alone.

DIAGNOSIS

Diagnosis is generally easy if the existence of the syndrome is known and the patient is able to describe his symptoms. The following criteria should be borne in mind. The sensations appear only when the patient is at rest, most often in the evening and early part of the night, and produce an irresistible need to keep the legs moving. Furthermore, the sensations are not felt in the skin but deep down inside the legs.

Although meralgia paraesthetica has been mistaken for restless legs, there is no resemblance between these two diseases.[4] Masland[22] has described myokymia as a cause of restless legs. I have also seen a few patients who have been irritated by myokymias in the legs, particularly in the calves. They resemble the fasciculations in amyotrophic lateral sclerosis but are of an innocent nature. This phenomenon has no relation to the syndrome of restless legs and should not be confused with it. Martin[23] has described a condition that he calls acroparesthesia in the lower limbs. He has, in my opinion, confused acroparesthesia and restless legs. It is beyond the scope of this paper to discuss all the different pathologic conditions associated with paresthesia or pain in the legs. In most cases, they are easily distinguished from restless legs.

Nevertheless, certain patients have symptoms which are more like those in restless legs syndrome than in any other condition but which present some atypical features. For example, the symptoms may be purely unilateral, or they may be felt during the whole day, even when the patient is in motion. They may be localized to the skin instead of deep inside the leg. The same diagnostic difficulty applies to other diseases in which the diagnosis is based essentially on the history. Migraine and trigeminal neuralgia, for instance, are well defined, easily recognizable syndromes. However, in practice, there are certain cases with more or less atypical features in which the diagnosis remains open to question. In the 175 cases on which the present paper is based, I have not included diagnostically uncertain cases with atypical features or cases in which the clinical picture was dominated by pain. It is especially the cases with pain which often have atypical features and may present great diagnostic difficulties. Details of these cases and a survey of the different kinds of paresthesias can be found in my monograph.[2] Growing pains in children may be a form of restless legs or an ailment related to this syndrome.[2]

ETIOLOGY

In most cases, the syndrome of restless legs occurs as an apparently independent disease with a course of many years' duration and no definitely known cause. Heredity is implicated,[2,13,14] because I have seen several families in which a dominant heredity seemed probable. I also have observed a pair of monozygotic twins who both had mild restless legs. Their mother had severe symptoms of the same kind. Restless legs often appear during the last half or trimester of pregnancy,[2,16,24] but, as a rule, the sensations disappear soon after delivery. The syndrome has also been observed in association with poliomyelitis[25] and other

infectious diseases, avitaminosis (burning-feet syndrome in prisoners of war in Japanese camps),[26] anemia of different types,[7,8,17–21,27] diabetes,[21] lengthy exposure of the legs to cold,[2] and intake of certain drugs (promethazine and prochlorperazine).

I found the incidence of restless legs in pregnant women to be 11%. In patients with iron deficiency (less than 60 μg. per 100 cc.), the incidence was 24%. In most cases, the symptoms were mild. Restless legs were the presenting symptom in 3 cases of carcinoma.[7]

PATHOGENESIS

Where and how the sensations develop is not known. Certain authors[16,18,28] consider that the disease originates in the spinal cord. Others[2,29] believe that there is a disturbance at some site in the limbs. The symptoms are relieved by vasodilator drugs, fever, and movement and are made worse by anemia. These facts indicate that there may be an accumulation of metabolites in the tissues as a result of anemia or local ischemia.

THERAPY

In those cases in which no etiologic factor such as anemia is demonstrable, the patient should be given a vasodilator drug for at least a month. In my experience, Priscoline (1 to 2 tablets three times a day), Ronicol (2 tablets three times a day), or carbachol (2 2-mg. tablets three times a day) ameliorates the creeping sensations in 2 out of 3 patients.[2,5] Carbachol and Priscoline gave improvement more often than placebos.[2] Good results have also been reported with Dilvasène[30] and Hexanicit (meso-inositol hexanicotinate).[31] If no improvement has taken place after a month, another of the aforementioned preparations should be tried instead. Sometimes, a certain medicine seems to be helpful for a time but is subsequently ineffective. It is therefore advisable to alternate different preparations.

If the symptoms are sporadic, nitroglycerin is worth a trial.[15] The dose is 0.5 to 1 mg. of nitroglycerin sublingually as soon as the creeping sensations start. This may give relief within a few minutes.

In patients with anemia due to iron deficiency, intravenous injection of iron has a good effect.[19] I have treated 10 patients with serum iron levels less than 60 μg. per 100 cc. with iron injections, and the results were highly satisfactory in every case. My experience with oral iron and with iron therapy in patients with normal serum iron is still limited. No contradiction is implied by the fact that both iron and vasodilator drugs are effective. In angina pectoris with sideropenia, improvement can result from both nitroglycerin and iron.[32]

Ascorbic acid,[33] aldehydes,[28] dextran,[19,20] and Arfonad, a histamine-liberator,[34] are other therapeutic media recommended. Unilateral lumbar sympathectomy was performed in one unusually severe case in my series. The leg became warmer, but the creeping sensations were not lessened.

In many cases, none of the aforementioned preparations is helpful. It is then necessary to resort to purely symptomatic therapy with analgesics, sedatives, and hypnotics. Such drugs may be effective, particularly in fairly mild cases. It should be remembered that promethazine makes the symptoms worse. In the really severe cases, barbiturates have no effect. Such patients state that they are unable to sleep despite large doses. They cannot stay in bed but stagger around the room like drunkards. One of my patients could not even keep on his legs but "crept around on the floor like a caterpillar." Some patients say that they never dare to take a sleeping drug because this prevents them from walking about at night, their only means of obtaining relief.

Narcotics such as codeine, dihydrocodeinone, opium, and Eucodal have a considerably better symptomatic effect than barbiturates. Opium was already used by Willis[10] (1685) with good results in one case. I have seen certain patients who have taken a narcotic orally every night for years. Some of them did not need to increase the dose. In a few cases, true narcomania, although of moderate degree, finally appeared, with gradually increasing doses. The use of narcotics should be avoided in restless legs syndrome. Once the patients have started to use them, they are extremely difficult to treat. Abstinence then exacerbates the leg symptoms. I nevertheless believe that it may sometimes be justified to give codeine or opium in desperate cases.

To sum up, it can be stated that some caution must be observed in judging the therapeutic results. Not only are the symptoms purely subjective, but spontaneous remissions occur. Certain patients, especially those with aching pain, are resistant to all hitherto known therapeutic media. Although the many mild cases require no specific therapy for their leg discomforts, it must be ascertained whether they are suffering from anemia or iron deficiency.

SUMMARY

The salient symptom of restless legs syndrome is unpleasant creeping sensations in the legs and, sometimes, the arms as well. They are not felt in the skin but deep inside, in the muscles or bones. They appear only during rest and produce an irresistible need to keep the limbs in motion. As a rule, there is no pain, but some patients have a dull ache. The symptoms generally occur in the evening and early part of the night and may be the cause of severe insomnia. The course is of many years' duration, sometimes with spontaneous remissions. All transitions from mild to extremely severe cases with almost complete insomnia are found.

The present paper is based on 175 personal cases, 72 men and 103 women. Nearly all the patients sought medical advice because of their leg discomforts alone. In many cases, one or several of the patient's relatives had restless legs. In most cases, examination disclosed nothing pathologic, but iron deficiency was found in 19 of 77 unselected patients. The symptoms may be exacerbated by anemia and iron deficiency. Restless legs were the initial symptom in 3 cases of carcinoma with sideropenia. Restless legs fairly often occur in the later stage of pregnancy. The pathogenesis is unknown, but the ailment is not psychogenic.

The sensations usually disappear in the presence of fever. Vasodilator drugs often have a favorable effect. In patients with iron deficiency, a course of iron injections generally produces improvement or cessation of the symptoms of restless legs.

REFERENCES

1. Ekbom, K. A.: Asthenia crurum paraesthetica (irritable legs). Acta med. scandinav. 118:197, 1944.
2. Ekbom, K. A.: Restless legs. Acta med. scandinav. supp. 158:1, 1945.
3. Ekbom, K. A.: Parästesier. Nord. med. 31:1651, 1946.
4. Ekbom, K. A.: Restless legs. J.A.M.A. 131:481, 1946.
5. Ekbom, K. A.: Restless legs, a report of 70 new cases. Acta med. scandinav. supp. 246:64, 1950.
6. Ekbom, K. A.: Restless legs. Svenska Läkartidn. 48: 862, 1951.
7. Ekbom, K. A.: Restless legs som tidigsymtom vid cancer. Svenska Läkardtidn. 52:1875, 1955.
8. Ekbom, K. A.: Restless legs hos blodgivare. Svenska Läkartidn. 53:3098, 1956.
9. Critchley, M.: The pre-dormitum. Rev. neurol. 93: 101, 1955.
10. Willis, T.: The London Practice of Physick. 1st ed., Thomas Bassett and William Crooke, London, 1685. p. 404
11. Wittmaack, T.: Pathologie und Therapie der Sensibilität-Neurosen. E. Schäfer, Leipzig, 1861. p. 459
12. Beard, G. M.: A Practical Treatise on Nervous Exhaustion, 2d ed. William Wood & Co., New York, 1880. pp 41-42
13. Oppenheim, H.: Lehrbuch der Nervenkrankheiten. 7th ed. S. Karger, Berlin, 1923. p. 1774
14. Mussio-Fournier, J. C., and Rawak, F.: Familiäres Auftreten von Pruritus, Urtikaria und parästhetischer Hyperkinese der unteren Extremitäten. Confinia neurol. 3:110, 1940.
15. Allison, F. G.: Obscure pains in the chest, back or limbs. Canad. M.A.J. 48:36, 1943.
16. Jolivet, B.: Paresthésies agitantes nocturnes des membres inférieurs, impatiences. Thèse de Paris, 1953.
17. Ask-Upmark, E., and Meurling, S.: On the presence of a deficiency factor in the pathogenesis of amyotrophic lateral sclerosis. Acta med. scandinav. 152: 217, 1955.
18. Ask-Upmark, E.: Contribution to the pathogenesis of the syndrome of restless legs. Acta med. scandinav. 164:231, 1959.
19. Nordlander, N. B.: Therapy in restless legs. Acta med. scandinav. 145:453, 1953.
20. Nordlander, N. B.: Restless legs. Brit. J. Phys. Med. 17:160, 1954.
21. Nordlander, N. B.: Orsaker till "restless legs." Svenska Läkartidn. 54:1159, 1957.
22. Masland, R. L.: Myokymia—cause of "restless legs." J.A.M.A. 134:1298, 1947.
23. Martin, J. P.: Acroparesthesia in the lower limbs: unexplained pains in the legs at night. Brit. M. J. 1: 307, 1946.
24. ten Berge, B. S.: Kuitkrampen en restless legs (anxietas tibiarum) in de zwangerschap. Geneesk. gids 31: 11, 1953.
25. Luft, R., and Müller, R.: "Crampi" och "restless legs" vid akut poliomyelit. Nord. med. 33:748, 1947.
26. Smitskamp, H.: A neuro-vascular syndrome related to vitamin deficiency. Thesis, Amsterdam, 1947.
27. Heden, S.: Restless leg hos blodgivare. Svenska Läkartidn. 54:609, 1957.
28. Brenning, R.: Restless legs. Svenska Läkartidn. 54: 2293, 1957.
29. Simons, A. J. R.: On paresthesiae. Thesis, Utrecht, 1951.
30. Bonduelle, M., and Jolivet, B.: Les impatiences. Bull. méd. (Paris) 67:316, 1953.
31. Lindqvist, T.: Klinisk prövning av Hexanicit, ett nikotinsyrapreparat med långvarig verkan. Svenska Läkartidn. 55:1, 1958.
32. Swedberg, B.: Anemi och sideropeni simulerande hjärtsjukdom. Svenska Läkartidn. 49:2591, 1952.
33. Wersall, J.: Restless legs. Svenska Läkartidn. 49: 2032, 1952.
34. Nordlander, N. B.: The use of a new histamine liberating substance, compound 48/80, in human subjects. Acta med. scandinav. 157:235, 1957.

A note on warm and cold spots

R. F. Kibler, M.D., and P. W. Nathan, M.D.

THUS FAR, two hypotheses have been put forward to account for the features of cutaneous sensibility: an older one based on the presence of morphologically distinct end organs, and a newer one holding that the important element of sensibility is the pattern set up in the central nervous system by the impulses conveyed by various nerve fibers.

The older hypothesis, usually associated with the names of von Frey and Goldscheider, proposes that there are certain basic modalities of sensation, each of which is subserved by a morphologically distinct end organ with its separate peripheral nerve fiber system. Stimulation of this end organ or its nerve fibers can give rise only to that modality of sensation subserved by this system.

The newer hypothesis has evolved largely from the recent work of Weddell and his associates.[1–6] They have shown that the previously described specific end organs are not necessary for the appreciation of these sensory modalities. In hairy skin, which covers more than 90% of the body, all organized or encapsulated endings may be absent and yet all forms of cutaneous sensibility are present. In the human lip, for instance, Hagen, Knoche, Sinclair, and Weddell[1] showed that "temperature sensibility is equally acute on either side of the red margin, that is, in both hairy and glabrous skin. No encapsulated nerve end-organs are seen in the hairy skin, but they abound in the mucous membrane." Weddell and his associates do not deny that warm and cold spots can be found, or, in other words, that the skin can be stimulated in such a way as to bring out in one small area a greater sensitivity to one kind of stimulation than to another, but they deny that this sensitivity is due to the presence of a morphologically distinct end organ. They do not deny the existence of some of the previously described end organs, but, since they found that all forms of sensation can be experienced without the presence of these end organs, they insist that such structures are not necessary for the appreciation of cutaneous stimuli. Although these authors do not seem to have considered what the function of the various described end organs is, it remains feasible to consider that they do play some role in providing information about the environment.

The new hypothesis this school proposes is that all the varieties of sensation that man can describe can be or are subserved ultimately by free nerve fibrils. The variables concerned are the number of fibers firing; the conduction rate of the fibers; their thresholds to stimulus intensity; their characteristics of refractoriness, adaptation, and after-discharge; and the frequency with which the fibers are induced to convey impulses. Any given nerve fiber is conceived as conveying impulses set off by various forms of stimulation. On this hypothesis, the recognition of the nature of a stimulus is a function of certain parts of the brain adapted to deal with spatial and temporal patterns of arriving impulses. Probably, the recognition of such patterns is learned during the early years of life, though the mechanism necessary for this function may be innate. It is envisaged that a stimulus with certain characteristics, such as tissue-damaging, heat-adding, and heat-subtracting stimuli, applied to the skin at a particular place gives rise to a unique pattern of impulses within the brain, and this evokes a psychical state called a sensation.

Goldscheider[7] has emphasized three points of evidence in support of the older hypothesis; they are not considered by Weddell and his school, as far as we know, and they would

From the Neurological Research Unit of the Medical Research Council, National Hospitals for Nervous Diseases, Queen Square, London.

Dr. Kibler, who is a Markle Scholar, is now with the Department of Medicine, University of Pittsburgh.

be difficult to explain on the newer hypothesis. They are:

1] Mechanical or painful stimuli, when applied to a warm spot, give rise to a sensation of warmth and, when applied to a cold spot, give rise to a sensation of cold.

2] Warm and cold spots, however they are stimulated, cannot give rise to sensations of touch and pain. Goldscheider says: "Whenever they are stimulated with stimuli, they answer with the sensation of temperature."

3] A warm spot stimulated by a cold stimulus gives rise to a sensation of warmth, and, vice versa, a cold spot stimulated by a warm stimulus gives rise to a sensation of cold. This third item is known as paradoxical stimulation.

If cold spots give rise to a sensation of cold whatever the stimulus and warm spots that of warmth whatever the stimulus and, more surprising, if each gives the specific modality of sensation when the exactly opposite kind of thermal stimulus is applied, this evidence accords very well with Goldscheider's hypothesis. However, according to Weddell's hypothesis, the nature of the stimulus is the all-important factor in determining the pattern of impulses arriving at the higher centers. It would seem unlikely, on this hypothesis, that there are warm and cold spots totally insensitive to mechanical and painful stimulation and even more unlikely that there are warm and cold spots giving paradoxical responses.

The evidence presented by Weddell and his readily and consistently give a thermal reassociates in support of their hypothesis is most convincing, but the three facts stressed by Goldscheider remain as strong supports for the older hypothesis and are difficult to explain on the new. Accordingly, we decided to repeat Goldscheider's experiments, carrying them out on normal subjects in the same manner that he had.

METHODS

Throughout this paper, we speak of warm and cold spots. Our doing so does not imply that we believe that such spots are anatomic entities; we regard them as artificialities consequent upon the method of testing. The spots are those small areas of skin which, on thermal testing in the manner described below, most sponse.

Before and throughout the investigation, many tests were done on ourselves; these were used as a guide to the testing of other subjects and will not be reported. The tests reported were conducted on 10 healthy adults who were ignorant of the purpose of this investigation.

The subjects rested in the laboratory for fifteen minutes to allow the temperature of their hands to become fairly constant. The part of the skin tested was on the backs of the hands, this skin having those characteristics associated with "hairy skin." If it was obviously hairy, it was shaved earlier in the day. The temperature of the stimulators was adjusted as the temperature of the hands changed during the course of a session. On one hand, 3 warm spots and, on the other, 3 cold spots were found by stimulation with the thermal stimulator described below. Only those spots that repeatedly gave a maximal warm or cold response were selected and were marked with colored ink; their presence was confirmed frequently during the session by application of the appropriate stimulus. Stimulation of the thermal spots and the regions between them was performed in a random order, the various forms of stimuli—mechanical, painful, and thermal—also being applied by hand in a random manner. During testing, it was often necessary to remind the subjects that they had to report all the sensations they were experiencing. Otherwise, they tended to concentrate on the thermal aspect of sensation and to omit any mention of the tactile aspects so obvious as to not require comment. All stimuli were applied while the subjects' eyes were closed. The stimulus was always applied for a duration of at least a second and was kept on the skin long enough for the subject to decide what sensation he was experiencing. The interval between stimulations was also fixed according to the wishes of the subject; he had to say when he was ready to be retested.

The stimulating instruments were drawn from two groups, one consisting of the instruments used by Goldscheider and the other consisting of these instruments modified as little as was found to be necessary. Since the purpose of this investigation was to repeat Goldscheider's work, the point was not to use instruments that we would consider better but to use the instruments Goldscheider used.

However, because we found during pilot experiments on ourselves and on some of the 10 subjects that these instruments were not modality specific, we were forced to modify them. We made only necessary changes, so as to keep the investigation as near the original one as possible. Our purpose was to see if Goldscheider's results could still be obtained with his instruments modified so as to be more modality specific, as he had probably intended them to be.

Goldscheider used sharpened wooden toothpicks and needles for nonthermal mechanical and painful stimulation. We added a small glass mercury skin thermometer because it could be used as both a purely mechanical thermally neutral stimulator and a thermal stimulator. The end of the thermometer had an area 4.9 sq. mm. When used as a thermally neutral mechanical stimulator, it was applied at the same temperature as the subject's skin, which was ascertained by means of a small thermojunction applied to the spot about to be stimulated. The mercury skin thermometer was kept in water at this temperature, quickly and thoroughly dried, and then applied. Thus, when the thermometer was used as a mechanical stimulator, care was taken that the stimulator neither added nor subtracted heat to or from the subject's skin. The same thermometer was used as a thermal stimulator applied at a known temperature difference from that of the subject's skin. This use of the end of the small mercury skin thermometer as warm, cold, and mechanical stimulator had the advantage that the mechanical aspects, touch and pressure, remained the same for all 3 types of stimulation. The only difference in the sensation experienced by the subject was a thermal one. The maximal warm stimulus was 46° C., and maximal cold was 5° C. It was found that stimuli less than 5° warmer or colder than the skin did not always cause a thermal response, so the stimulus was considered to be a thermal one only when it was more than 5° different from the temperature of the subject's skin.

RESULTS

The results of testing 10 subjects on warm and cold spots with thermal, mechanical, and painful stimuli are given in Tables 1 and 2. In order to present the results in this tabular form, it has been necessary to condense or even modify some of the responses of the subjects. For example, the needle would sometimes be felt immediately as pain. At other times, it would be felt as touch or pressure, going on to pain. In all such cases, the response has been regarded as one of "only pain" because we are concerned here only with the differences between thermal and other qualities and not with the sensations of touch, pressure, or pain. From the two tables, the following information is obtained.

A cold stimulus applied to a warm spot never gave a sensation of warmth, and a warm stimulus applied to a cold spot never gave a sensation of cold. In 482 stimulations of thermal spots in 10 subjects, paradoxical responses were not found.

Painful stimulation never gave a thermal sensation on warm or cold spots; it gave only a painful sensation.

All the thermal stimuli and all the mechanical stimuli always gave a sensation of touch or pressure. In the case of the thermal stimuli, this was in addition to a thermal sensation when applied to thermal spots.

A thermally neutral mechanical stimulus applied to cold spots gave a sensation of cold only once in 1 subject out of a total of 81 stimulations in 10 subjects.

A thermally neutral mechanical stimulus applied to warm spots sometimes gave a sensation of warmth. This did not occur consistently, as it did when a warm stimulus was applied to a warm spot. Often, the mechanical stimulation of a warm spot would give rise to a delayed response of warmth. When a mechanical stimulus was applied to one warm spot successively without intervening stimulation of other parts of the skin, the first response might be found to be touch and warmth, the next touch and very slight warmth coming on with a slight delay, and, later, purely touch responses. Such a result was common. By contrast, a warm stimulus to a warm spot consistently gave a ready and quick response of warmth, although, with repeated warm stimuli to one spot, the response tended to be less and less intense. Mechanical stimulations of warm spots noticeably elicited an indeterminate warm response, the subjects saying: "Touch; possibly warm too." In 1 subject, H.H., the

TABLE 1
SENSATION ON STIMULATION OF WARM SPOTS
Kinds of stimuli and responses from stimulating warm spots

Subject	*Mechanical cold stimulus gave sensation of*			*Mechanical thermally neutral stimulus gave sensation of*		*Painful stimulus gave sensation of*	
	warmth or heat	*cold*	*only touch or pressure*	*touch or pressure and warmth or heat*	*only touch or pressure*	*pain and warmth or heat*	*only pain*
E. C.	0/10	8/10	2/10	1/10	9/10	0/10	10/10
J. H.	0/8	7/8	1/8	5/10	5/10	0/5	5/5
J. C.	0/7	6/7	1/7	4/18	14/18	0/7	7/7
B. S.	0/10	9/10	1/10	0/7	7/7	0/7	7/7
G. E.	0/9	9/9	0/9	0/4	4/4	0/4	4/4
R. C.	0/10	10/10	0/10	7/10	13/20	0/5	5/5
J. K.	0/10	10/10	0/10	0/7	7/7	0/6	6/6
L. K.	0/7	6/7	1/7	1/18	17/18	0/7	7/7
P. G.	0/2	2/2	0/2	0/7	7/7	0/10	10/10
H. H.	0/3	3/3	0/3	1/15	14/15	0/2	2/2

Figures indicate ratio of responses to stimulations

sharpened toothpick applied to a warm spot drew a response that has been recorded as warmth; the actual words used were "touch and pressure; slightly painful warmth, may really be pain."

Apart from the evidence presented in the tables, other points related to the two hypotheses deserve mention. The morphologic end organ hypothesis seems to demand far more definite spots than one finds. Further, a warm or cold spot is far too big to be a minute point covering the known size of the morphologic end organs. In fact, these spots are not so much spots as regions of maximum sensitivity in a large area of good sensitivity. It may be considered that Weddell's hypothesis substitutes area sensitivity for minute punctate sensitivity, and this, in our opinon, fits in better

TABLE 2
SENSATION ON STIMULATION OF COLD SPOTS
Kinds of stimuli and responses from stimulating cold spots

Subject	*Mechanical warm stimulus gave sensation of*			*Mechanical thermally neutral stimulus gave sensation of*		*Painful stimulus gave sensation of*	
	cold	*warmth or heat*	*touch or pressure*	*touch or pressure and cold*	*only touch or pressure*	*pain and cold*	*only pain*
E. C.	0/14	6/14	8/14	0/8	8/8	0/10	10/10
J. H.	0/7	6/7	1/7	0/7	7/7	0/5	5/5
J. C.	0/9	7/9	2/9	1/12	11/12	0/7	7/7
B. S.	0/9	2/9	7/9	0/7	7/7	0/7	7/7
G. E.	0/18	7/18	11/18	0/4	4/4	0/4	4/4
R. C.	0/8	3/8	5/8	0/14	14/14	0/5	5/5
J. K.	0/12	3/12	9/12	0/7	7/7	0/6	6/6
L. K.	0/4	0/4	4/4	0/9	9/9	0/7	7/7
P. G.	0/4	1/4	3/4	0/6	6/6	0/10	10/10
H. H.	0/6	2/6	4/6	0/7	7/7	0/2	2/2

Figures indicate ratio of responses to stimulations

with what is observed. A further point to be mentioned is that spots sensitive to warmth are less definite and harder to find than spots sensitive to cold.

Apart from observations related to the two hypotheses, certain other points deserve mention. As shown in Table 1, only certain subjects experienced a sensation of warmth from tactile stimulation. That is to say, not all subjects experienced it on rare occasions; 4 never experienced it, 3 experienced it only once, and 3 experienced it on many occasions.

On nearly all occasions, a cold stimulus applied to a warm spot was found to give rise to a sensation of cold, and a warm stimulus applied to a cold spot often caused a sensation of warmth. Thus, the nervous arrangement beneath a spot that is particularly sensitive to one of these kinds of stimulation is also sensitive to some extent to the other kind. Spots particularly sensitive to warm stimulation were also most sensitive to cold stimulation, but spots particularly sensitive to cold stimulation were less frequently also sensitive to warm stimulation. It must be admitted, however, that our warm stimulus was often 5° to 12° higher than the skin temperature, whereas our cold stimulus was often 20° below it.

We also gained the impression that the actual temperature applied to a cold spot, provided it was 5° or more below the skin temperature, was unimportant. With the small area stimuli used, an all-or-none cold response was elicited immediately, however cold the stimulus was, but, on the warm spot, the actual temperature applied was important. The response seemed to be graded in accordance with the amount of heat imparted to the skin.

DISCUSSION

We will first give Goldscheider's conclusions and state how ours differ from his. We will then consider the possible causes for the differences and, finally, will discuss other relevant matters.

1] Goldscheider found that a cold stimulus applied to a warm spot gives the sensation of warmth and that a warm stimulus applied to a cold spot gives the sensation of cold. In 482 thermal stimulations in 10 subjects, this paradoxical response was never found.

2] Goldscheider found that warm spots give a sensation of warmth, however they are stimulated. Although we could not confirm this, we found that a thermally neutral mechanical stimulus applied to warm spots gave a sensation of warmth in 19 out of 116 stimulations in 10 subjects. In many respects, this sensation of warmth differed from the invariable warmth response elicited when a warm stimulus was applied; these differences have been mentioned already. We did not find that warm spots give a sensation of warmth, no matter how they are stimulated, because this response never occurred with a cold stimulus or needles.

3] Goldscheider found that cold spots give a sensation of cold, however they are stimulated. We could not confirm this but found that a thermally neutral mechanical stimulus elicited a sensation of cold on a cold spot once out of 81 stimulations in 10 subjects.

4] Goldscheider found that warm and cold spots are insensitive to touch and pain. In no subject was this ever found by us. All mechanical stimulations of any part of the back of the hand, including the warm and cold spots, were felt as touch or pressure, and all pricks with a needle caused pain.

In attempting to explain the differences between our own and these earlier results, we can only put forward some suggestions. We are unable to understand the earlier finding of paradoxical stimulation or the obtaining of warm and cold responses from stimulating thermal spots with needles, and we cannot understand how Goldscheider found cold and warm spots insensitive to painful and mechanical stimulation.

Perhaps Goldscheider obtained thermal responses to mechanical stimulation because his mechanical stimulators were in fact not thermally neutral. We found that the metal and glass needles were certainly not thermally neutral. Little rods of wood or toothpicks, such as were used by Goldscheider, although poor conductors of heat, were often felt as cold because, if applied at room tmperature, they were usually sufficiently colder than the skin to be felt as cold on a cold-sensitive spot. When these stimulators were used as purely mechanical stimuli, it was found to be unsatisfactory to adjust their temperature to that of the subject's skin by placing them in water at the required temperature, since, when they

were applied at a temperature 1 or 2° higher than the subject's skin temperature, they were sometimes felt as cold, presumably because heat was subtracted from the skin to evaporate the moisture remaining on the wood. For reasons such as these, we had to abandon Goldscheider's methods of stimulation and use the same stimulus for mechanical, warm, and cold stimulation, the only difference in the stimulus being its thermal properties. Goldscheider may have found, as we did, that, sometimes, when a thermal spot is stimulated with a thermal stimulus and then restimulated with a mechanical stimulus, the later stimulation calls forth a combined thermal and tactile response. A third mechanical stimulation of the same spot gives only a tactile response. This is likely to occur when the stimuli are applied without an adequate rest period between each or when other regions of skin are not stimulated between the applications of stimuli to the thermal spots. Such responses are more likely to occur in some subjects than in others; for instance, as seen in Table 1, 5 out of 10 mechanical stimulations elicited thermal responses in subject J.H. On each of these occasions, these mechanical stimulations followed a thermal stimulation of the thermal spot.

However, we do not think that phenomena such as these, which might be considered spurious results, explain all the warmth responses to mechanical stimulations; we still obtained such responses when we took care to stimulate other regions between the stimulation of the thermal spots and to leave a sufficient period of rest between reapplication of thermal and mechanical stimuli to the same spot.

To us, the fact that previous stimulation affects subsequent results in the ways mentioned above indicates that this is a central nervous phenomenon related to facilitation or some manifestation of central control and that it cannot be interpreted solely in terms of the peripheral end organ in the skin. To a subject being tested, it is obvious that central nervous factors, those called "attention" in psychologic parlance, play an important role in the situation of observing sensations induced by punctate stimulations. Further, attention can be directed not only to a region and a point within that region but also to a modality of sensation and any chosen aspect of the sensation evoked by a stimulus. Indeed, it is difficult for a subject to report the total impression received and not to concentrate on certain aspects of the sensation aroused by a stimulus. Clearly, attention (whatever central nervous functioning subserves it) can be made use of by the subject to counteract the possible effects of adaptation of the peripheral mechanism. A subject can feel a constant stimulus or not as he chooses, according to the amount of attention he fixes on the point stimulated.

The investigation of cutaneous sensation in man has often been undertaken on the conscious or unwitting assumption that small punctate kinds of stimulations are particularly suited to demonstrate the essential peripheral elements of sensibility. However, such artificially simplified forms of stimulation are devoid of biologic significance, having played no role in the evolution of mammals. Moreover, the idea that the ultimate peripheral sensory unit can be tested in conscious man without the participation of the central nervous system is obviously erroneous. In this situation, the investigator may be testing the subject's ability to interpret the pattern of impulses arriving at high levels of the central nervous system and his ability to express this in words rather than testing the primary elements of reception in the skin and conduction to the spinal cord which underlie sensibility.

SUMMARY

Hypotheses put forward to explain cutaneus sensibility are:

1] That each of four basic modalities of sensation are subserved by a morphologic structure with its own set of nerve fibers, stimulation of which can cause only that modality of sensation subserved

2] That all the varieties of cutaneous sensation can be, or are, subserved ultimately by free nerve fibrils and that no encapsulated structures with nerve fibers specifically devoted to one modality of sensation are necessary. Evidence brought forward by Goldscheider in support of the first hypothesis included the fact of paradoxical stimulation of warm and cold spots and the fact that warm

and cold spots are insensitive to other forms of stimulation, being capable only of registering warm or cold. On the second hypothesis, such facts are most difficult to account for.

We were unable to confirm that paradoxical stimulation exists, that warm and cold spots are insensitive to mechanical and painful stimulation, or that cold spots give a sensation of cold when painfully or mechanically stimulated. However, we were able to confirm that warm spots may give a sensation of warmth when mechanically stimulated but only in certain subjects and rarely in them. We therefore conclude that this important evidence favoring the first hypothesis cannot be substantiated.

The authors take this opportunity to thank Dr. E. A. Carmichael for the facilities for doing this work and for his interest and criticisms.

REFERENCES

1. Hagen, E., Knoche, H., Sinclair, D. C., and Weddell, G.: The role of specialized nerve terminals in cutaneous sensibility. Proc. Roy. Soc., London B 141:279, 1953.
2. Sinclair, D. C., Weddell, G., and Zander, E.: The relationship of cutaneous sensibility to neurohistology in the human pinna. J. Anat. 86:402, 1952.
3. Lele, P. P., Weddell, G., and Williams, C. M.: The relationship between heat transfer, skin temperature and cutaneous sensibility. J. Physiol. 126:206, 1954.
4. Weddell, G., Pallie, W., and Palmer, E.: The morphology of peripheral nerve terminations in the skin. Quart. J. Micr. Sci. 95:483, 1954.
5. Weddell, G.: Somesthesis and the chemical senses. Ann. Rev. Psychol. 6:114, 1955.
6. Zander, E., and Weddell, G.: Observations on the innervation of the cornea. J. Anat. 85:68, 1951.
7. Goldscheider, A.: Physiologie der Hautsinnesnerven. Leipzig, J. A. Barth, 1898.

AMYTAL® provides uniform daytime sedation

Clinically, Amytal has been shown to be valuable in the treatment of psychoneurosis. In a comparative study of fifty-one psychoneurotic outpatients with tension, Amytal was superior to all other agents tested.[1]

The duration of effect of Amytal is about eight to eleven hours, an action span particularly valuable for daytime sedation. It also offers the additional advantages of greater safety, since it is metabolized and does not depend on the kidneys for elimination. Therefore, renal damage does not constitute a contraindication.

The usual dosage is 1/4 grain four times a day.

Available in tablets of 1/4, 1/2, 3/4, and 1 1/2 grains, and in elixirs containing 2 grains and 4 grains per ounce.

Amytal® (amobarbital, Lilly)

1. Brit. M. J., *2*:63, 1957.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

"R Day"

for the neuritis patient can be tomorrow

"R Day"—*when pain is relieved*—can come early for patients with inflammatory (non-traumatic) neuritis if treatment with Protamide is started promptly after onset.

Protamide is the therapy of choice for either early or delayed treatment, but early use assures greatest efficacy.

For example, in a 4-year study[1] and a 26-month study[2] a combined total of 374 neuritis patients treated with Protamide during the first week of symptoms responded as follows:

60% required only 1 or 2 daily injections for complete relief

96% experienced excellent or good results with 5 or less injections

Thus, the neuritis patient's first visit—especially an early one—affords the opportunity to speed his personal "R Day."

Protamide is available at pharmacies and supply houses in boxes of ten 1.3 cc. ampuls. Intramuscularly only, one ampul daily.

PROTAMIDE®

REFER TO PDR
PAGE 813

Sherman Laboratories
Detroit 11, Michigan

1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

IN THE SAME PATIENT...

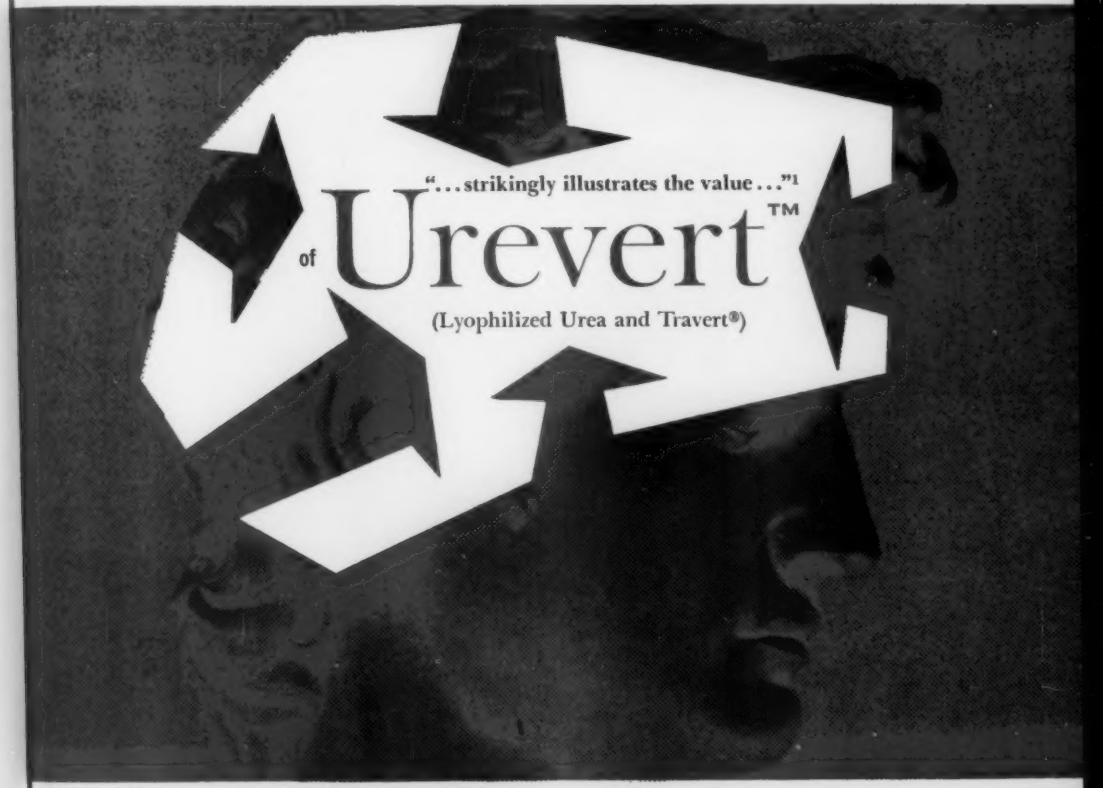
WITHOUT UREVERT

"Prior to the use of urea for intracranial decompression . . . the patient was admitted for cranioplasty because of a left cranial defect. During the operation the brain began to expand . . . it was necessary to reduce . . . pressure by lumbar puncture. The total operating time was two hours and twenty minutes."[1]

WITH UREVERT

"Recently this patient was readmitted for cranioplasty of the right side. In this operation urea [Urevert] was used. . . . Cranioplasty was easily accomplished. No lumbar puncture was necessary. The operating time was fifty minutes."[1]

CRANIOPLASTY OPERATION TIME WAS REDUCED BY 1-1/2 HOURS!



The New, Superior[1,2] Intracranial Decompressant

"The use of urea [Urevert] for brain decompression often simplifies and extends the limits of neurosurgical procedures and, in some patients, proves to be life-saving."

New Sound-Color Film—The new approach to the reduction of intracranial pressure with Urea-Invert sugar (Urevert) is herein described and illustrated. Conditions so treated include glioblastoma multiforme, optic nerve glioma, frontotemporal meningioma, cerebellar astrocytoma and retrogasserian rhizotomy. Film showings may be arranged by writing to Medical Film Library, Travenol Laboratories, Inc., Morton Grove, Illinois.

1. Taheri, Z. E.: Urevert in Cranial Trauma and Brain Surgery, J. Internatl. College of Surgeons *32*:389 (Oct.) 1959.
2. Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, Aug. 1958, p. 907.

TRAVENOL LABORATORIES, INC.

Pharmaceutical Products Division of
BAXTER LABORATORIES, INC.
Morton Grove, Illinois

Stelazine®

brand of trifluoperazine

to help you reach the chronic psychotic

Because of its clinically demonstrated effectiveness in the treatment of chronic psychotics, 'Stelazine' therapy should be tried for such patients, no matter how discouraging the results of previous therapies may have been.

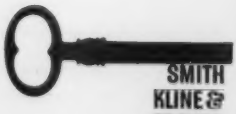
an awakening effect

Allen[1] reports that 'Stelazine' had an awakening effect on chronic patients "who had previously been lacking ambition, initiative, or interest in their surroundings."

delusional and hallucinatory trends alleviated

'Stelazine' also "alleviated delusional and hallucinatory trends and facilitated communication and psychotherapy. . . . To appreciate the significance of this progress, it must be remembered that these patients had spent years on closed wards, beyond the reach of any available form of therapy."

1. Allen, V. S.: Trifluoperazine in the Treatment of Drug-Resistant Schizophrenics, J. Clin. & Exper. Psychopath. *20*:247 (Sept.) 1959.



SMITH KLINE & FRENCH

leaders in psychopharmaceutical research

a new film

"Soma in Cerebral Palsy"

by Catherine E. Spears, M.D.

WALLACE LABORATORIES is pleased to announce the availability of the 16 mm., color film, SOMA IN CEREBRAL PALSY.

Photographed at the Children's Country Home in Westfield, New Jersey, and narrated by Dr. Spears, this 14-minute sound film presents the results of the preliminary clinical trials with the new muscle relaxant, SOMA[T.M.] (carisoprodol Wallace).

Four children were selected for this presentation. They are representative not only of the type and degree of handicap seen at this center, but also of the progress attained with the help of SOMA.

Copies of the film for showing to medical groups may be obtained by writing to the Professional Services Department, Wallace Laboratories, New Brunswick, New Jersey.

WALLACE LABORATORIES
NEW BRUNSWICK, NEW JERSEY

NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

SEPTEMBER 1960

Augustus S. Rose, M.D., President
A. L. Sahs, M.D., President-Elect
Joseph M. Foley, M.D., Vice-President
Robert Utterback, M.D., Secretary
Charles M. Poser, M.D., Treasurer

Symposium on Abnormal Nervous Function Conducted in Boston

On June 12 through 14, 1960, a symposium on abnormal nervous function was held under the auspices of the University of Maryland at the Statler-Hilton Hotel, Boston. The central theme of the symposium concerned the physiologic, metabolic, and behavioral aspects of neural abnormality. Among the distinguished foreign participants in the program were J. C. Eccles (Australia), S. Thesleff (Lund), and Gray Walter (Bristol). Among AAN members who participated were Karl Frank (Bethesda); H. W. Magoun (Los Angeles); H. H. Jasper (Montreal); J. K. Merlis (Baltimore); A. Earl Walker (Baltimore); J. Mendelson (Boston); H. Kluver (Chicago); M.A.B. Brazier (Boston); I. Tasaki (Bethesda); R. Brady (Bethesda); R. Grenell (Baltimore); B. Chance (Philadelphia); and D. Lindsley (Los Angeles). The symposium was summarized by R. G. Grenell, and the proceedings will be published in Progress in Neurobiology....The symposium was supported by the National Institute of Neurological Diseases and Blindness with a supplement from the Upjohn Company, Kalamazoo, Mich.

MS Society Meets in Boston

The National Multiple Sclerosis Society convened in the Statler-Hilton Hotel in Boston for the Twenty-eighth Semiannual Meeting of its Medical Advisory Board (June 15, 1960). Thomas L. Willmon, Medical and Research Director, opened the meeting with a few remarks before handing the gavel to the Society's newly elected Chairman, Roland P. Mackay, who introduced distinguished guests Professor Katzuki of Kiyushi University and Dr. Murray Bornstein of New York, as well as the new members of the Medical Advisory Board, Richard Paddison, Charles Kunkle, and Richard P. Schmidt. Allan Bailey was also there as liaison member of the Canadian Neurological Society....After Chairman Mackay's opening remarks, reports were given on the Society's research review panel activities by Harry Zimmerman, on Canadian Society activities by Allan Bailey, on the NINDB drug therapy symposium by George Schumacher, and on the general status of the Society by Thomas L. Willmon. The final report, accompanied by lively discussions, was given by Murray B. Bornstein on the application of tissue culture to the study of demyelinization.

Board Schedules 1961 Examinations David A. Boyd, Jr., Executive Secretary of the American Board of Psychiatry and Neurology, announces that 2 board examinations have been scheduled for 1961. The first will be conducted in New Orleans (March 20 and 21, 1961) and the second in Chicago (October 9 and 10, 1961)....All inquiries should be directed to Dr. David A. Boyd, Jr., Executive Secretary-Treasurer, American Board of Psychiatry and Neurology, 102-110 Second Avenue S. W., Rochester, Minn.

Woolsey Elected To National Academy At its Ninety-seventh Annual Meeting (April 26), the National Academy of Sciences announced the election of 35 new members on the basis of their distinguished and continued achievements in original research. Among those to be awarded what is considered to be one of the highest honors that can be visited upon an American scientist was AAN member Clinton M. Woolsey, Research Professor of Neurophysiology, Medical School and Graduate School, University of Wisconsin. Dr. Woolsey also is a member of the Advisory Council of the National Institute of Neurological Diseases and Blindness.

Neuropathologists Elect Richter as New President At the Thirty-sixth Annual Meeting of the American Association of Neuropathologists, Richard Richter (Chicago) was elected President for 1961. Other 1961 officers are David Cowen (New York), President-Elect; Karl Neurberger (Denver), Vice President; Leon Roizin (New York), Secretary-Treasurer; and Irwin Feigin (New York), Assistant Secretary-Treasurer.

Merlis New President of EEG Society At the June 1960 meeting of the American Electroencephalographic Society in Cape Cod, Mass., Jerome K. Merlis was elected President, succeeding Arthur A. Ward, Jr. Other newly elected officers were Charles E. Henry, President-Elect; George A. Ulett, Secretary; and Isadore S. Zfass, Treasurer....All inquiries should be addressed to Dr. George A. Ulett, Secretary, American EEG Society, Washington University School of Medicine, 1420 Grattan Street, St. Louis 4.

AACP To Meet in Pittsburgh The Annual 1960 Meeting of the American Academy for Cerebral Palsy will take place in Pittsburgh's Penn-Sheraton Hotel (October 5 through 7). This year's program will highlight an entire half-day devoted to a panel discussion on fundamentals and clinical methods of management of involuntary movements. Also to be featured are the usual instructional courses and a series of round table discussions

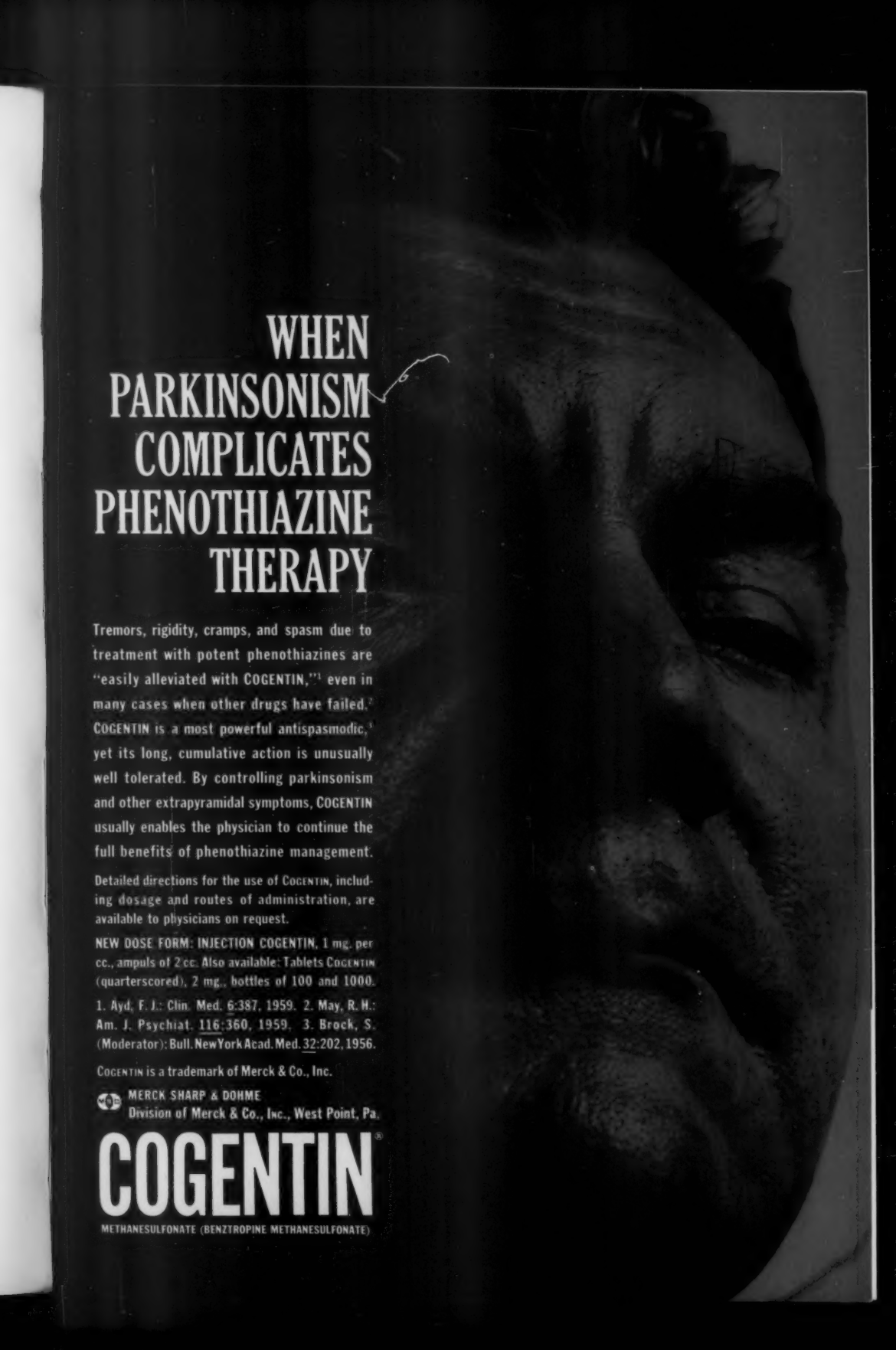
(limited to 15) on pertinent facts in cerebral palsy. Advance registrations may be made through Dr. J. D. Russ, Secretary, 1520 Louisiana Avenue, New Orleans 15....The AACP membership was shocked to learn of the recent death (May 19) of Dr. Herman Josephy, one of their most faithful members and workers, who, at the time of his death, was Vice President of the Society. The unexpired term of Dr. Josephy, who also was an AAN member, was recently filled by Dr. Jessie Wright of Pittsburgh.

Here and There The 1960 annual meeting of the Association of American Medical Colleges will be held October 30 through November 1 at the Diplomat Hotel, Hollywood Beach, Fla.... At New York's Montefiore Hospital, there is a tissue bank containing 8,000 specimens of human brain and spinal cord, 200 of them from multiple sclerosis victims. The Director of the bank, Harry M. Zimmerman, states that researchers throughout the world -- Denmark, Norway, Israel, Union of South Africa, and Japan, as well as the United States -- are being supplied on request vital tissue specimens from this reservoir....President Eisenhower has signed into law a bill setting up a new program of international medical research within the office of the NIH Director, Dr. James A. Shannon. Purpose of the program is to support planning for research for disease and disease prevention on a world-wide basis and encourage international coordination of medical research programs. The program is to be financed largely through U.S.-owned foreign currencies obtained from surplus farm commodities sent abroad. The bill is a cutdown version of Senator Hill's (D.,Ala.) and Representative Fogarty's (D., R.I.) proposal for a National Institute of International Medical Research but is considered as an expression of congressional approval of international medical research....NIH's new building, for its Division of Biologics Standards, was dedicated on June 30 in Bethesda by Thailand's visiting King, Bhumidol Adulyadej, American-born son of a physician trained at Harvard....On July 24 through 27, about 50 neurologists from many countries convened to participate in the First International Symposium on the Parasitoses of the Nervous System, conducted under the auspices of the Institute of Neurology of the University of Brazil and the Society of Neurology of Rio de Janeiro. The sessions were organized and conducted by Professor Deolindo Couto, Professor of Neurology of the University of Brazil and Director of the Institute.

Briefs Wilder Penfield has resigned as head of the Montreal Neurological Institute to embark on a second career of writing and medical education under the Guggenheim Fellowship Program. His successor at Montreal is Theodore Rasumussen....At present, approximately 900 trainees in neurologic sciences in

institutions are supported by NINDB grants; of these, about 283 are in clinical neurology....Future AAN programs will include an index of authors....The 1961 AAN meeting is scheduled to be held at the Sheraton-Cadillac Hotel in Detroit, the 1962 meeting at the Statler-Hilton Hotel in New York, and, for 1963, Denver is being seriously considered....Orville Bailey has been appointed Chairman of the AAN Section of Neuroanatomical Sciences to fill the vacancy created by the resignation of Paul Yakovlev. Ray S. Snider remains Secretary....The Academy mourns the recent death (July 21) of one of its most beloved members, William G. Lennox. He was 76 years old.

Rose Bailey



WHEN PARKINSONISM COMPLICATES PHENOTHIAZINE THERAPY

Tremors, rigidity, cramps, and spasm due to treatment with potent phenothiazines are "easily alleviated with COGENTIN,"[1] even in many cases when other drugs have failed.[2] COGENTIN is a most powerful antispasmodic,[3] yet its long, cumulative action is unusually well tolerated. By controlling parkinsonism and other extrapyramidal symptoms, COGENTIN usually enables the physician to continue the full benefits of phenothiazine management.

Detailed directions for the use of COGENTIN, including dosage and routes of administration, are available to physicians on request.

NEW DOSE FORM: INJECTION COGENTIN, 1 mg. per cc., ampuls of 2 cc. Also available: Tablets COGENTIN (quarterscored), 2 mg., bottles of 100 and 1000.

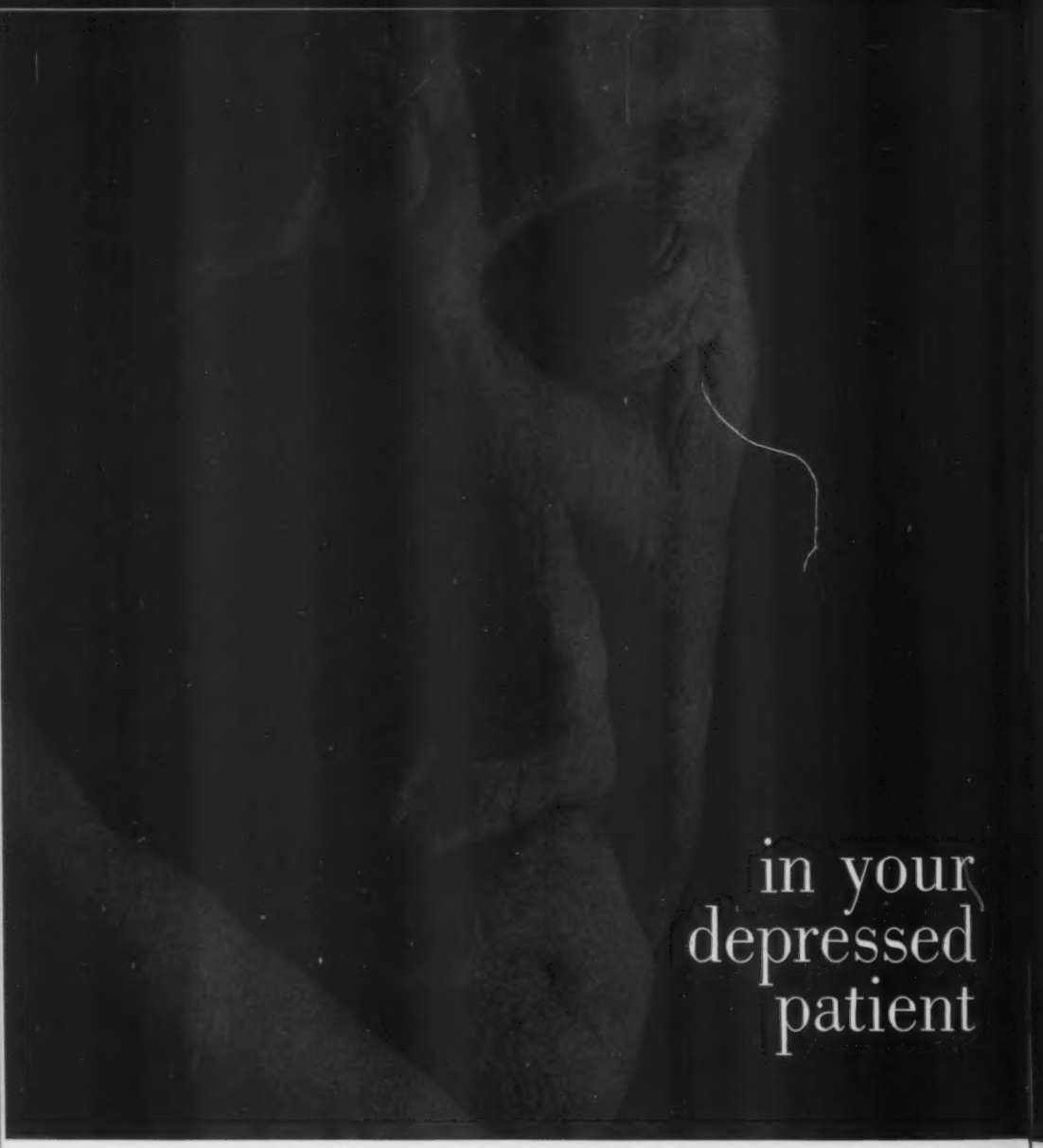
1. Ayd, F. J.: Clin. Med. 6:387, 1959. 2. May, R. H.: Am. J. Psychiat. 116:360, 1959. 3. Brock, S. (Moderator): Bull. New York Acad. Med. 32:202, 1956.

COGENTIN is a trademark of Merck & Co., Inc.

MERCK SHARP & DOHME
Division of Merck & Co., Inc., West Point, Pa.

COGENTIN®

METHANESULFONATE (BENZTROPINE METHANESULFONATE)



remove the depression with new *a true antidepressant* Nardil™

brand of phenelzine dihydrogen sulfate

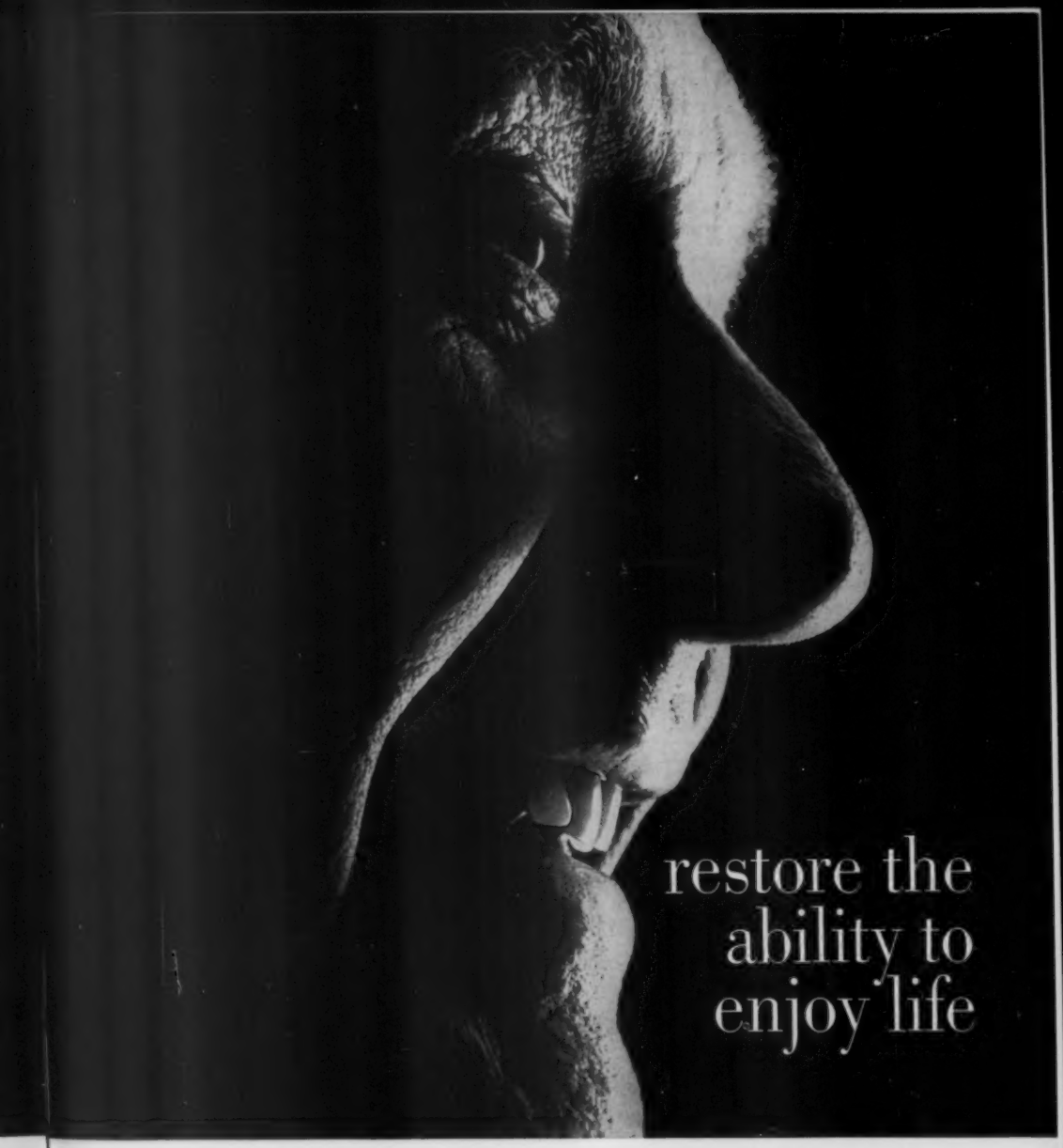
rapidly effective—antidepressant response often within a few days; complete remission usually within 2 to 6 weeks, in 4 out of 5 patients.[1-10]

low toxicity—no significant reports of toxicity to liver, blood or kidneys.[1-10]

corrective—helps remove the depression, rather than merely masking the symptoms... restores the mild-to-deeply depressed patient without institutionalization and without recourse to ECT in most cases.[1-10]

simple dosage—1 tablet 3 times a day.

PHI



INDICATIONS: Mild to severe depressions, depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis. Improves the depressed phase of affective (manic-depressive) psychosis, and relieves the depression of catatonic schizophrenics, although not affecting the psychosis *per se*. SIDE EFFECTS: Occasional postural hypotension and infrequent nausea, ankle edema, delayed micturition or constipation are managed by appropriate adjunctive therapy, or dosage reduction. DOSAGE: One tablet three times a day. After remission, reduce to a maintenance level of 1 or 2 tablets a day. SUPPLIED: Orange-coated tablets, each containing 15 mg. of phenylethylhydrazine present as the dihydrogen sulfate. Bottles of 100. CAUTION: Nardil should be withheld or used with extreme caution where the patient has a history of liver disease or liver damage is present. Hypotensive patients should be under close medical supervision.

REFERENCES: 1. Sainz, A.: *Ann. New York Acad. Sc.* **80**:780, Art. 3 (Sept. 17) 1959. 2. Thal, N.: *Dis. Nerv. System* **20**:197 (May, Pt. 1) 1959. 3. Saunders, J. C., Kline, N. S., *et al.*: *Am. J. Psychiat.* **116**:71, 1959. 4. Arnow, L. E.: *Clinical Med.* **6**:1573, 1959. 5. Dickel, H. A., *et al.*: *Clinical Med.* **6**:1579, 1959. 6. Dunlop, E.: *Rhode Island M. J.* **42**:656, 1959. 7. Sainz, A.: *Dis. Nerv. System* **20**:537, 1959. 8. Sarwer-Foner, G. J., *et al.*: *Canad. M.A.J.* (in press) 1959. 9. Hobbs, L. E.: *West Virginia M. J.* (in press) 1959. 10. Dunlop, E.: *Dis. Nerv. System* (in press) 1959.

WARNER CHILCOTT
MORRIS PLAINS, N.J.

HALL-BROOKE HOSPITAL

An Active Treatment Hospital Located one hour from New York

Accredited by:

The Central Inspection Board of the American Psychiatric Association
The Joint Commission on Accreditation of Hospitals

HALL-BROOKE, GREENS FARMS, BOX 31, CONN.

Telephone: WESTPORT CAPITAL 7-1251

George S. Hughes, M.D.
Leo H. Berman, M.D.
Albert M. Moss, M.D.
Louis J. Micheels, M.D.
Robert Isenman, M.D.
John D. Marshall, Jr., M.D.
Edward M. Keelan, M.D.
Peter P. Barbara, Ph.D.

CARE and TRAINING for the MENTALLY RETARDED CHILD

The Training School at Vineland provides care and treatment for boys and girls 2 years or older with mental potential of 6 years. Complete professional staff. Electroencephalographic, and neurological examinations, individual psychiatric, psychological, physiological, and speech observations and therapies.

SIX COMPREHENSIVE PROGRAMS:

- **Observation and Diagnosis**
- **Education and Training**
- **Custodial Care**
- **Residential Supervision**
- **Summer Program**
- **Psychiatric Treatment Center**

The educational program aims at maximum development of each child. Training includes self-care; group living; formal classroom education; development of practical habits, attitudes and work skills. Children live in homelike cottages on 1600-acre estate. School, hospital, chapel, swimming pools, lake, working farm. The Training School Research Laboratory is famed for continuous study of causes, prevention and treatment of mental retardation. Established 1888. For information write: Registrar, Box Q,

THE TRAINING SCHOOL AT VINELAND, NEW JERSEY

A private, non-profit residential center for the care and treatment of the mentally retarded

complete integrated facilities for

ELECTROMYOGRAPHY

- **SINGLE CHANNEL EMG** with two-channel magnetic tape recorder for recording notes and EMG simultaneously. — Model TE 1.2-7
- **TWO-CHANNEL EMG** permits simultaneous recording and study of two EMG potentials or of one potential together with a related physical parameter such as force or pressure. — Model TE 2-7

• Automatic controls and new circuits provide simplified reliable operation without shielded rooms in most locations. • EMG potentials faithfully reproduced by special recorder circuits. • Specifications equal or surpass requirements for research, teaching and clinical use.

NEW rugged COAXIAL NEEDLE ELECTRODE withstands autoclaving, has tapered shaft, 26 gauge at tip, insulated handle.

TECA CORPORATION

80 Main St.
White Plains
New York

DRUG-INDUCED PARKINSONISM IS ON THE RISE,
reflecting the growing use of potent tranquilizers. These extrapyramidal disturbances may be reduced by lowering tranquilizer dosage.

***"It is almost always preferable, however, to merely add oral AKINETON®... since this avoids the risk of loss of therapeutic benefit and permits uninterrupted phenothiazine therapy."**

AKINETON®

BRAND OF BIPERIDEN

a prompt, specific countermeasure to drug-induced akinesia
motor restlessness · akathisia · torticollis · oculogyric crises · chorea

remarkably safe — "Akineton was not responsible for a single dangerous or toxic effect in the 500 patients treated."*

Dosage: Doses required to achieve the therapeutic goal are variable and individually adjusted. The following are average doses.

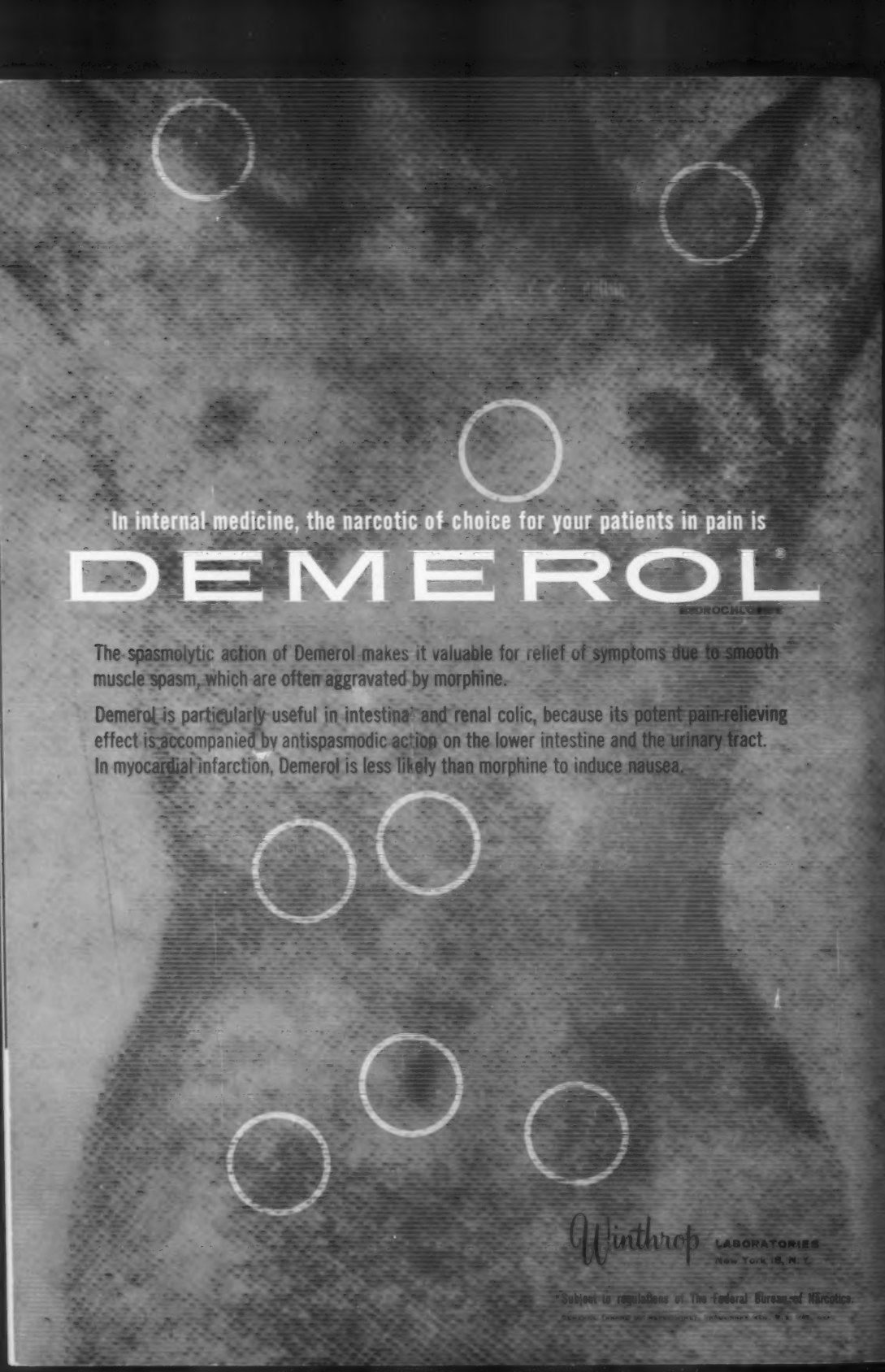
Drug-induced extrapyramidal disorders
1 tablet (2 mg.) one to three times daily

Parkinson's disease
1 tablet (2 mg.) three or four times daily

AKINETON hydrochloride tablets—2 mg., bisected, bottles of 100 and 1000.

*Ayd, Frank J., Jr.: Drug-induced Extrapyramidal Reactions: Their Clinical Manifestations and Treatment with Akineton. Psychosomatics 1:143 (May-June) 1960.

KNOLL PHARMACEUTICAL COMPANY, ORANGE, NEW JERSEY


In internal medicine, the narcotic of choice for your patients in pain is
DEMEROL®
The spasmolytic action of Demerol makes it valuable for relief of symptoms due to smooth muscle spasm, which are often aggravated by morphine.
Demerol is particularly useful in intestinal and renal colic, because its potent pain-relieving effect is accompanied by antispasmodic action on the lower intestine and the urinary tract. In myocardial infarction, Demerol is less likely than morphine to induce nausea.
Winthrop LABORATORIES
New York 18, N. Y.
Subject to regulations of the Federal Bureau of Narcotics.